PROCEEDINGS
OF THE
ROYAL SOCIETY OF MEDICINE
Vol. 45 No. 12 December 1952

CONTENTS

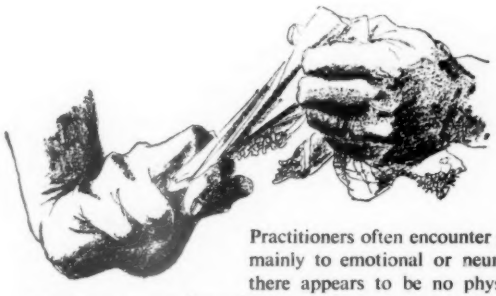
Whole Proceedings Page

Section of Medicine
DISCUSSION ON THE COLLAGEN VASCULAR DISEASES 811

Section of Laryngology with Section of Otology
JOINT SUMMER MEETING WITH THE NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY HELD AT MANCHESTER ROYAL INFIRMARY
LARYNGOLOGICAL SESSION
Bilateral Abductor Paralysis: Arytenoidectomy for Bilateral Abductor Paralysis—Extralaryngeal Approach.—DE GRAAF WOODMAN, M.D. 821
Mixed Salivary Tumours of the Upper Respiratory Tract.—Professor VICTOR LAMBERT, F.R.C.S. 826
Bucco-pharyngeal Ulceration of Undetermined Ætiology [*Abridged*].—KENNETH HARRISON, F.R.C.S. 828
The Significance of Alveolar Osteitis in Rhinology.—H. G. BEDFORD RUSSELL, F.R.C.S., and LESLIE WRIGHT, L.R.C.P., M.R.C.S., L.D.S. 830

Section of Urology
May 22, 1952
DISCUSSION ON THE CHRONICALLY DILATED URETER [*Abridged*] 835
June 26, 1952
DISCUSSION ON THE TREATMENT OF ANURIA 844

Continued overleaf



Nervous Exhaustion

Practitioners often encounter patients whose ill-health is due mainly to emotional or neurotic disturbance. Frequently there appears to be no physical basis and their principal symptoms are usually undue nervousness, fatigue and poor appetite.

For these mildly neurasthenic and exhausted cases 'BEPLETE' Wyeth is uniquely appropriate. It contains Phenobarbitone and Vitamin B-complex as an appetising Elixir, and so provides a quieting relaxation, while at the same time supplying nutritional factors known to be essential for the energy requirements of nervous metabolism.

'BEPLETE' contains:— *Phenobarbitone B.P. ¼gr.: Aneurine Hydrochloride 1.5 mg.: Riboflavin 1.0 mg.: Pyridoxine Hydrochloride 0.33 mg.: Nicotinamide B.P. 10.0 mg.: Pantothenyl Alcohol 0.2 mg. (equivalent to 0.212 mg. Pantothenic Acid): Alcohol 15%.*

'Beplete'
Trade Mark

John Wyeth & Brother Ltd., Clifton House, Euston Road, London, N.W.1. Wyeth

CONTENTS (*continued*)

Whole Proceedings Page

Section of Pædiatrics

May 23, 1952
CASES 857–862

June 28, 1952
MEETING HELD AT THE RADCLIFFE INFIRMARY, OXFORD
Tension Cysts of the Lung [*Abstract*].—G. C. LAURIE PILE, F.R.C.S. 863
Experiences with Retrolental Fibroplasia in Oxford.—MARY W. COXON, M.B., D.C.H. 863
The Factor of Inheritance in Convulsive Disorders in Childhood [*Abridged*].—CHRISTOPHER OUNSTED, D.M., D.C.H. 865

JOINT MEETING NO. 6
Section of Psychiatry with Section of Anæsthetics
DISCUSSION ON NEW MUSCLE RELAXANTS IN ELECTRIC CONVULSION THERAPY 869

Books Received for Review. Books Recently Presented and Placed in the Society's Library 880

Clinical Section
MEETING HELD AT QUEEN MARY'S HOSPITAL FOR CHILDREN, CARSHALTON, SURREY 881
Section of Orthopædics
The Syndrome of Forefoot Instability.—R. C. F. CATTERALL, F.R.C.S. 891
Clinical Applications of the Functional Anatomy of the Lower Back [*Summary*].—W. F. FLOYD, Ph.D., B.Sc., F.Inst.P., A.M.I.E.E., J. S. R. GOLDING, F.R.C.S., and P. H. S. SILVER, M.B., Ph.D. 894
Section of Epidemiology and State Medicine
DISCUSSION ON THE CAUSES OF ABSENCE FROM SCHOOL 895

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Copyright: The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors. All papers, &c., presented at meetings (other than those which have been previously published) are held to be subject to the Society's copyright until a decision in regard to their publication has been made.

Announcing

AN EFFECTIVE ALTERNATIVE TO THE BARBITURATES

'OBLIVON'

3-methyl-pentyne-ol-3

FOR THE RAPID INDUCTION OF SLEEP WITHOUT 'HANGOVER'

'OBLIVON', 3-methyl-pentyne-ol-3, is an entirely new product with a chemical structure quite distinct from that of the barbiturates.

While it induces sleep quickly and effectively, 'Oblivon' is non-toxic even in dosage very much higher than that required for therapeutic purposes. It is almost completely eliminated from the body within two hours, so that a 'hangover' effect or cumulative toxicity is impossible.

'Oblivon' is indicated whenever quick induction of sleep is required. There are no contra-indications to the use of 'Oblivon' and it may be used in conditions where other sleep-inducing drugs would be contra-indicated.

Presentation: 'Oblivon' is presented in capsules containing 250 mg. 3-methyl-pentyne-ol-3 in containers of 25 and 100.

Dose: Two 250 mg. capsules will be found to be effective within fifteen to thirty minutes after administration in the majority of cases.

FULL LITERATURE AND SAMPLES AVAILABLE ON REQUEST

British Schering Limited

Kensington High Street, London, W.8

telephone: WEstern 8111

Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

[*March* 25, 1952]

DISCUSSION ON THE COLLAGEN VASCULAR DISEASES

Dr. A. H. T. Robb-Smith: In this Discussion we would appear to have restricted the field by the title "Collagen Vascular Diseases", and yet instead of considering atherosclerosis and cystic medial necrosis of the aorta, we shall discuss disseminate lupus, dermatomyositis, polyarteritis nodosa, &c., in which the vascular lesions are only part of the general disturbance of connective tissue. It would be possible to describe the histological appearances in these conditions, but in a brief discussion such a review would of necessity be superficial and not very informative, and so it would seem more profitable to put forward some ideas as to the morphogenesis of these conditions, but it should be emphasized that they are largely speculative and not grounded on much factual evidence.

If we accept as a postulate, and I think we must, that the morphological changes in these conditions are a reflection of a disturbance of connective tissue formation, it is well to consider what we know about the normal formation of connective tissue.

Connective tissue is the extracellular framework which lies between the cells and consists of the scleroprotein fibres, collagen, reticulin and elastica, lying in a matrix of so-called ground substance which is rich in mucopolysaccharides. There has been much argument as to whether collagen fibres are formed within fibroblasts or not, but the general, though not universal, view nowadays is that they are formed extra-cellularly though the fibroblast has something to do with their formation, but the problem which only recently is beginning to be resolved is the relationship between the mucopolysaccharides and the collagen fibres, for a relationship there clearly is even though collagen has a very low carbohydrate content.

Under the light microscope collagen fibres are arranged in bundles and appear to merge with the finer fibres which are known as reticulin (Fig. 1). With the electron microscope the finest collagen

FIG. 1.—Spleen stained to show reticulin and collagen fibrils. × 1,000.

CONTENTS (*continued*)

Whole Proceedings Page

Section of Pædiatrics

May 23, 1952

CASES 857–862

June 28, 1952

MEETING HELD AT THE RADCLIFFE INFIRMARY, OXFORD

Tension Cysts of the Lung [*Abstract*].—G. C. LAURIE PILE, F.R.C.S. 863

Experiences with Retrolental Fibroplasia in Oxford.—MARY W. COXON, M.B., D.C.H. 863

The Factor of Inheritance in Convulsive Disorders in Childhood [*Abridged*].—CHRISTOPHER OUNSTED, D.M., D.C.H. 865

JOINT MEETING NO. 6

Section of Psychiatry with Section of Anæsthetics

DISCUSSION ON NEW MUSCLE RELAXANTS IN ELECTRIC CONVULSION THERAPY 869

Books Received for Review. Books Recently Presented and Placed in the Society's Library 880

Clinical Section

MEETING HELD AT QUEEN MARY'S HOSPITAL FOR CHILDREN, CARSHALTON, SURREY 881

Section of Orthopædics

The Syndrome of Forefoot Instability.—R. C. F. CATTERALL, F.R.C.S. 891

Clinical Applications of the Functional Anatomy of the Lower Back [*Summary*].—W. F. FLOYD, Ph.D., B.Sc., F.Inst.P., A.M.I.E.E., J. S. R. GOLDING, F.R.C.S., and P. H. S. SILVER, M.B., Ph.D. 894

Section of Epidemiology and State Medicine

DISCUSSION ON THE CAUSES OF ABSENCE FROM SCHOOL 895

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Copyright: The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors. All papers, &c., presented at meetings (other than those which have been previously published) are held to be subject to the Society's copyright until a decision in regard to their publication has been made.

Announcing

AN EFFECTIVE ALTERNATIVE TO THE BARBITURATES

'OBLIVON'

3-methyl-pentyne-ol-3

FOR THE RAPID INDUCTION OF SLEEP WITHOUT 'HANGOVER'

'OBLIVON', 3-methyl-pentyne-ol-3, is an entirely new product with a chemical structure quite distinct from that of the barbiturates.

While it induces sleep quickly and effectively, 'Oblivon' is non-toxic even in dosage very much higher than that required for therapeutic purposes. It is almost completely eliminated from the body within two hours, so that a 'hangover' effect or cumulative toxicity is impossible.

'Oblivon' is indicated whenever quick induction of sleep is required. There are no contra-indications to the use of 'Oblivon' and it may be used in conditions where other sleep-inducing drugs would be contra-indicated.

Presentation: 'Oblivon' is presented in capsules containing 250 mg. 3-methyl-pentyne-ol-3 in containers of 25 and 100.

Dose: Two 250 mg. capsules will be found to be effective within fifteen to thirty minutes after administration in the majority of cases.

FULL LITERATURE AND SAMPLES AVAILABLE ON REQUEST

British Schering Limited

Kensington High Street, London, W.8

telephone: WEstern 8111

Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

[*March* 25, 1952]

DISCUSSION ON THE COLLAGEN VASCULAR DISEASES

Dr. A. H. T. Robb-Smith: In this Discussion we would appear to have restricted the field by the title "Collagen Vascular Diseases", and yet instead of considering atherosclerosis and cystic medial necrosis of the aorta, we shall discuss disseminate lupus, dermatomyositis, polyarteritis nodosa, &c., in which the vascular lesions are only part of the general disturbance of connective tissue. It would be possible to describe the histological appearances in these conditions, but in a brief discussion such a review would of necessity be superficial and not very informative, and so it would seem more profitable to put forward some ideas as to the morphogenesis of these conditions, but it should be emphasized that they are largely speculative and not grounded on much factual evidence.

If we accept as a postulate, and I think we must, that the morphological changes in these conditions are a reflection of a disturbance of connective tissue formation, it is well to consider what we know about the normal formation of connective tissue.

Connective tissue is the extracellular framework which lies between the cells and consists of the scleroprotein fibres, collagen, reticulin and elastica, lying in a matrix of so-called ground substance which is rich in mucopolysaccharides. There has been much argument as to whether collagen fibres are formed within fibroblasts or not, but the general, though not universal, view nowadays is that they are formed extra-cellularly though the fibroblast has something to do with their formation, but the problem which only recently is beginning to be resolved is the relationship between the mucopolysaccharides and the collagen fibres, for a relationship there clearly is even though collagen has a very low carbohydrate content.

Under the light microscope collagen fibres are arranged in bundles and appear to merge with the finer fibres which are known as reticulin (Fig. 1). With the electron microscope the finest collagen

FIG. 1.—Spleen stained to show reticulin and collagen fibrils. × 1,000.

CONTENTS (*continued*)

Whole Proceedings Page

Section of Pædiatrics

May 23, 1952

CASES 857–862

June 28, 1952

MEETING HELD AT THE RADCLIFFE INFIRMARY, OXFORD

Tension Cysts of the Lung [*Abstract*].—G. C. LAURIE PILE, F.R.C.S. 863

Experiences with Retrolental Fibroplasia in Oxford.—MARY W. COXON, M.B., D.C.H. 863

The Factor of Inheritance in Convulsive Disorders in Childhood [*Abridged*].—CHRISTOPHER OUNSTED, D.M., D.C.H. 865

JOINT MEETING NO. 6

Section of Psychiatry with Section of Anæsthetics

DISCUSSION ON NEW MUSCLE RELAXANTS IN ELECTRIC CONVULSION THERAPY 869

Books Received for Review. Books Recently Presented and Placed in the Society's Library 880

Clinical Section

MEETING HELD AT QUEEN MARY'S HOSPITAL FOR CHILDREN, CARSHALTON, SURREY 881

Section of Orthopædics

The Syndrome of Forefoot Instability.—R. C. F. CATTERALL, F.R.C.S. 891

Clinical Applications of the Functional Anatomy of the Lower Back [*Summary*].—W. F. FLOYD, Ph.D., B.Sc., F.Inst.P., A.M.I.E.E., J. S. R. GOLDING, F.R.C.S., and P. H. S. SILVER, M.B., Ph.D. 894

Section of Epidemiology and State Medicine

DISCUSSION ON THE CAUSES OF ABSENCE FROM SCHOOL 895

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Copyright: The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors. All papers, &c., presented at meetings (other than those which have been previously published) are held to be subject to the Society's copyright until a decision in regard to their publication has been made.

Announcing

AN EFFECTIVE ALTERNATIVE TO THE BARBITURATES

'OBLIVON'

3-methyl-pentyne-ol-3

FOR THE RAPID INDUCTION OF SLEEP WITHOUT 'HANGOVER'

'OBLIVON', 3-methyl-pentyne-ol-3, is an entirely new product with a chemical structure quite distinct from that of the barbiturates.

While it induces sleep quickly and effectively, 'Oblivon' is non-toxic even in dosage very much higher than that required for therapeutic purposes. It is almost completely eliminated from the body within two hours, so that a 'hangover' effect or cumulative toxicity is impossible.

'Oblivon' is indicated whenever quick induction of sleep is required. There are no contra-indications to the use of 'Oblivon' and it may be used in conditions where other sleep-inducing drugs would be contra-indicated.

Presentation: 'Oblivon' is presented in capsules containing 250 mg. 3-methyl-pentyne-ol-3 in containers of 25 and 100.

Dose: Two 250 mg. capsules will be found to be effective within fifteen to thirty minutes after administration in the majority of cases.

FULL LITERATURE AND SAMPLES AVAILABLE ON REQUEST

British Schering Limited

Kensington High Street, London, W.8

telephone: WEstern 8111

Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

[*March* 25, 1952]

DISCUSSION ON THE COLLAGEN VASCULAR DISEASES

Dr. A. H. T. Robb-Smith: In this Discussion we would appear to have restricted the field by the title "Collagen Vascular Diseases", and yet instead of considering atherosclerosis and cystic medial necrosis of the aorta, we shall discuss disseminate lupus, dermatomyositis, polyarteritis nodosa, &c., in which the vascular lesions are only part of the general disturbance of connective tissue. It would be possible to describe the histological appearances in these conditions, but in a brief discussion such a review would of necessity be superficial and not very informative, and so it would seem more profitable to put forward some ideas as to the morphogenesis of these conditions, but it should be emphasized that they are largely speculative and not grounded on much factual evidence.

If we accept as a postulate, and I think we must, that the morphological changes in these conditions are a reflection of a disturbance of connective tissue formation, it is well to consider what we know about the normal formation of connective tissue.

Connective tissue is the extracellular framework which lies between the cells and consists of the scleroprotein fibres, collagen, reticulin and elastica, lying in a matrix of so-called ground substance which is rich in mucopolysaccharides. There has been much argument as to whether collagen fibres are formed within fibroblasts or not, but the general, though not universal, view nowadays is that they are formed extra-cellularly though the fibroblast has something to do with their formation, but the problem which only recently is beginning to be resolved is the relationship between the mucopolysaccharides and the collagen fibres, for a relationship there clearly is even though collagen has a very low carbohydrate content.

Under the light microscope collagen fibres are arranged in bundles and appear to merge with the finer fibres which are known as reticulin (Fig. 1). With the electron microscope the finest collagen

FIG. 1.—Spleen stained to show reticulin and collagen fibrils. × 1,000.

fibres are seen to have a cross-striated appearance and the striation has a definite periodicity of 640Å., and this is true of all natural collagens. It is important to realize the great increase in magnification that one gains with the electron microscope and yet to remember that a great gap exists between the images of the electron microscope and the molecular structure of collagen.

Keith Porter (1952), at the Rockefeller Institute, has been studying the formation of collagen in tissue culture. If plasma and embryonal extract is used as the nutrient medium, the fibres that form in relation to the fibroblasts have the normal structure of collagen with the 640Å. period, but if the nutrient medium merely consists of Locke's solution and bouillon, although fibres are formed during the few days the cultures grow, they have an abnormal periodicity, a uniform banding at 210Å., and only a few fibres of the 640Å. period are seen to develop (Fig. 2), and on occasions fibres with a very much larger period, 1,100Å. (Fig. 3), are formed. These 210Å. fibres have on occasion been observed in embryonic material in man, but the importance of this work is that we have evidence that under abnormal conditions of metabolism, collagen fibres are formed which are structurally abnormal.

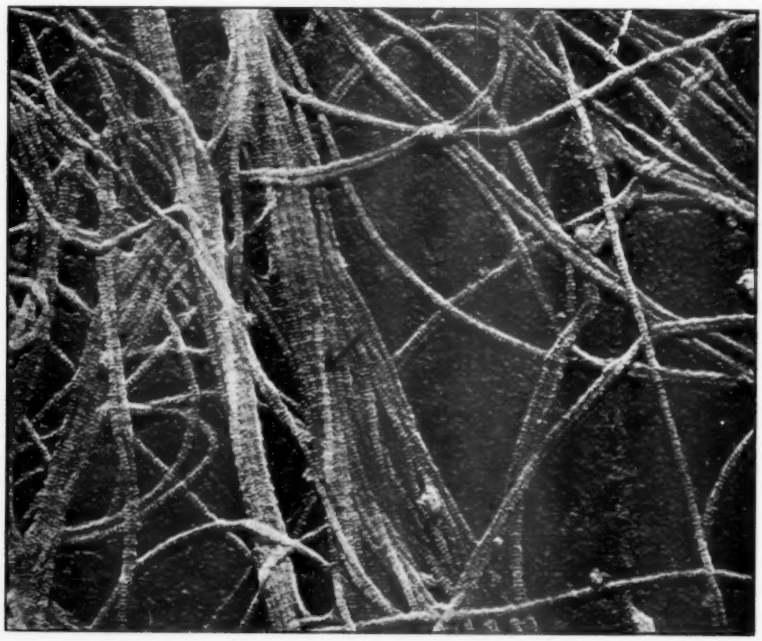


FIG. 2.—Electron micrograph of tissue culture of chick embryo skin grown in plasma-free medium. The majority of collagen fibrils have a periodicity of 210Å., but at the point marked with an arrow, fibres are developing the 640° periodicity. (*From* Porter, 1952.) × 30,000

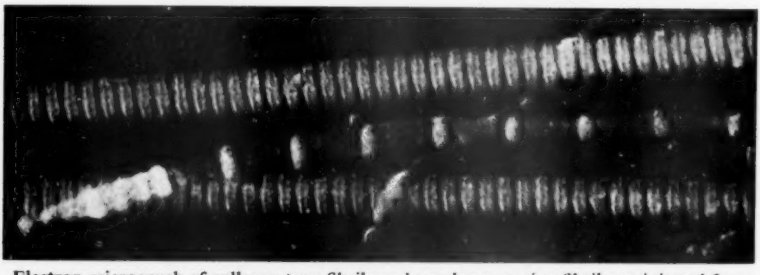


FIG. 4.—Electron micrograph of collagen type fibrils and one long spacing fibril precipitated from a mixture of plasma mucoprotein and acetic acid solution of ichthyocol. (*From* Highberger *et al.*, 1951.) × 44,000

Another aspect of work on the formation of collagen has arisen from studies of the material first isolated by a group of Russian scientists and called by them procollagen; it is obtained by dialysis of a citric acid extract of skin and on examining this material with the electron microscope, it is found to contain a mixture of the normal 640Å. collagen fibres and fibres with a very long spacing 2,000–3,000 Å. Now, if collagen is purified, none of this long spacing collagen is formed, and it occurred to Highberger, Gross and Schmitt (1951) that one stage of the purification might remove mucoprotein; they added mucoprotein to purified collagen, and, according to the concentration, they produced varying proportions of long spacing or normal spacing collagen fibres (Fig. 4); furthermore acid polysaccharides, such as hyaluronic acid or heparin, did not induce fibre formation but only glucoproteins derived from plasma.

So we have experiments—test-tube experiments, it is true—which point to the fact that glucoproteins from plasma may play a part in the formation of both normal and abnormal collagens.

Now Fischer (1947) has put forward a hypothesis, supported by experimental work, that the plasma proteins form a readily available source of amino-acids for the synthesis of complex cellular and extracellular protein, that the plasma proteins are broken down by proteolytic enzymes of the fibrinolysin or plasma trypsin type or else are fixed on to cells by a mechanism analogous to that occurring in blood coagulation and so are readily accessible to cellular proteolytic enzymes; thus the complex systems of enzymes and inhibitors and clotting factors may play a fundamental part in cellular protein synthesis and the process of blood coagulation in the prevention of hæmorrhage may merely be a caricature of their true physiological significance.

One of the objections to this hypothesis of transpeptidization catalysed by proteolytic enzymes is that enzymes of this type also catalyse the hydrolysis of the peptides and the competition between water and the amine for the carboxyl group will almost certainly be decided in favour of water, as the hydrolysis equilibrium of all peptides is far to the side of complete hydrolysis; however, in connective tissue the mucopolysaccharides are very active in water binding and so water might not enter in competition and thus transpeptidization might proceed.

Now, turning to the basic pathological processes that may be involved, it is necessary to consider Eppinger's concept of serous inflammation. In essence this postulates that, as the result of damage to capillary endothelium, cell membranes or ground substance, there is an accumulation of a protein-rich fluid in the connective tissue spaces and the consequent separation of the capillary from the parenchyma impairs the transport of nutritive materials and cellular metabolites with a secondary

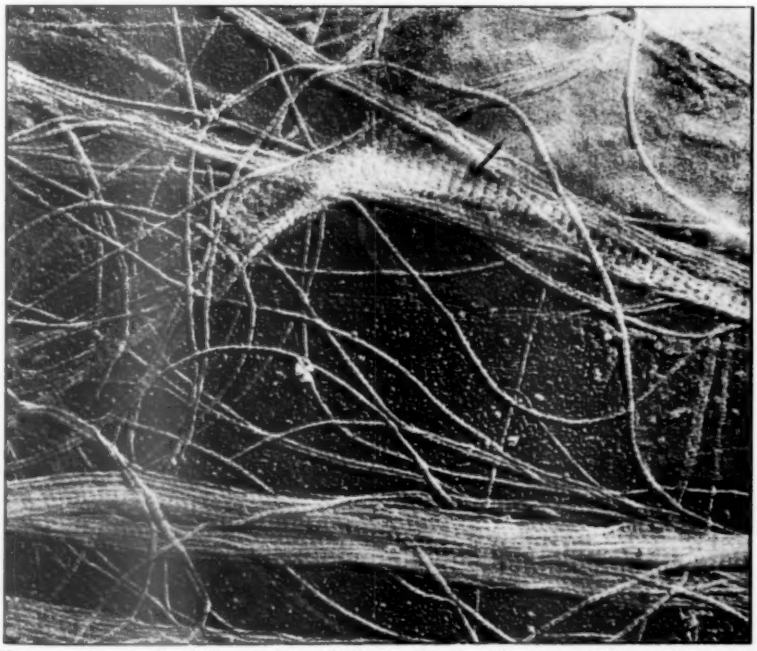


FIG. 3.—Electron micrograph of tissue culture similar to Fig. 2. The arrow indicates large period fibres. (*From* Porter, 1952.) × 18,000

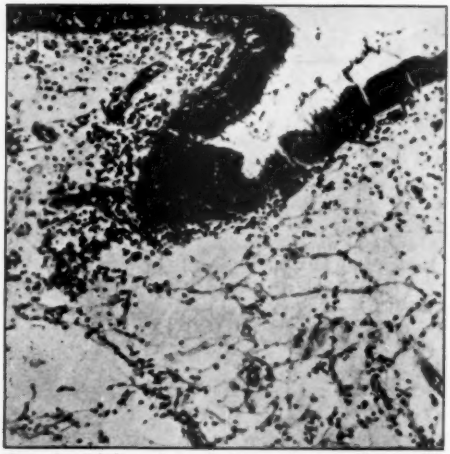


FIG. 5.—Lining of nasal sinus. Acute œdema with wide separation of connective tissue fibres. ×120

FIG. 6.—Lining of nasal sinus. Resolution of acute œdema with partial collapse of connective tissue and hyalinization of deeper layers. ×120

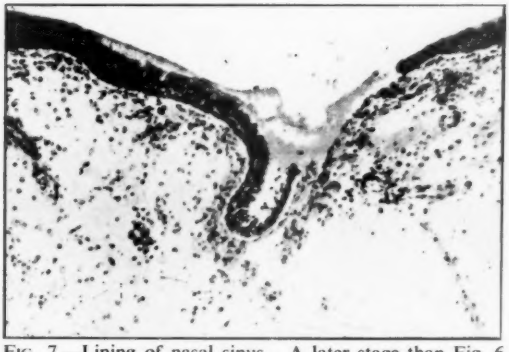


FIG. 7.—Lining of nasal sinus. A later stage than Fig. 6 but showing the same healing process. ×120

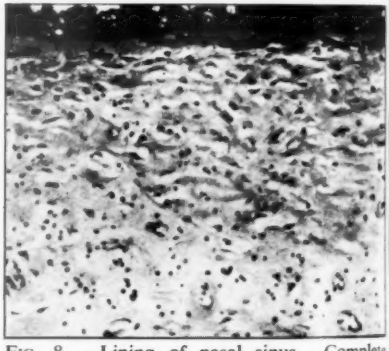


FIG. 8.—Lining of nasal sinus. Complete hyalinization of submucosa. ×120

Acknowledgments.—Figs. 2 and 3 are reproduced by permission of the Josiah Macy, Jr., Foundation, and Fig. 4 by permission of the Editor of the *Proceedings of the National Academy of Sciences*.

disturbance of cellular function. I must emphasize again the functional and metabolic importance of the connective tissue; all extracellular metabolic processes must be mediated through this layer of connective tissue which may in some places be only a few hundred Ångstrom thick but formed of a mucopolysaccharide complex of great lability with an intercommunicating system of protein fibres whose energy surface is immense and may well have great electronic mobility. It is only necessary to consider the speed of action of drugs or poisons to realize the functional activity of the connective tissue and it is equally obvious that if, as a result of accumulation of fluid, the hæmato-parenchymal space is increased, it will have profound effects on the body's metabolism.

The type of damaging influence to produce a serous inflammation is immaterial, though it is clear that different agents will produce differing metabolic effects. However, at the level of the light microscope one can say that the basic change is an accumulation not only of protein but also an increase of mucopolysaccharides which are revealed by their metachromatic staining by toluidine blue.

The source of the tissue mucopolysaccharides is in doubt but it may be that they are synthesized through the mediation of mast cells which ordinarily store the non-acetylated form—heparin. If the damaging agent is of low toxicity or transient in its action, the process is reversible, but as the lesions become more chronic the œdematous metachromatic tissue is converted into a non-fibrillary collagen lipoid complex—hyaline. This can easily be demonstrated in many tissue reactions and a familiar example is the changes in the lining of the nasal sinuses (Figs. 5–8).

Turning to more specific processes, Oberling (1943) found that injections of denatured plasma proteins induced in connective tissue the deposition of extra-cellular material resembling hyaline, amyloid and fibrinoid and he postulated that the so-called tissue degenerations resulted from enzymatic denaturation of proteins which were deposited in the tissues but had induced no antigenic response; his evidence for a lack of immunological reactivity of these denatured proteins was poor, but Pirani and Catchpole (1951) have shown that subscorbutic animals develop amyloidosis associated with an increase of serum glucoproteins; they have suggested that ascorbic acid deficiency induces a depolymerization of the ground substance and the glycoproteins which are released form complexes with plasma globulin and this is precipitated in the form of amyloid.

Engel has shown the effect of parathormone on bone, which can be a purely local action, is a depolymerization of the bone substance with a rise of serum glycoproteins and the deposition of carbohydrate casts in the kidney; he suggests that the changes in calcium and phosphorus metabolism may be secondary to this primary effect.

Teilum (1952) has approached an analogous problem from a slightly different standpoint. He has suggested that the normal mesenchymal reaction to an abnormal protein is the proliferation of plasma cells with the formation of antibody globulin and this would normally undergo involution to a hyaline or healing stage but that under certain conditions, possibly as the result of the formation of abnormal tissue enzymes or excess adreno-cortical activity, the healing process does not take place and instead there is the development of amyloid, and he has shown that ascorbic acid and cortisone are antagonists in this morphological counterpart of Selye's Adaptation Syndrome.

Now, what evidence have we that these mechanisms of abnormal glycoprotein formation are associated with the morphogenesis of the so-called collagen diseases. I think there is quite a lot.

In disseminate lupus erythematosus, there is an abnormal material—a fibrinoid—in the connective tissue, changes in the glomerular basement membrane and the presence of hæmatoxylinophil bodies in the tissues; there are changes in the serum proteins and glycoproteins and some alterations in the serum enzymes. Klemperer *et al.* (1950) have shown that the hæmatoxylinophil bodies are denatured nucleoproteins and recently have suggested that the fibrinoid change is associated with a more extreme nucleoprotein denaturation. The factor in the serum, described by Haserick, which induces the formation of "L.E. cells" has been shown to be antigenic and present in the globulin fraction and there have been *in vitro* observations of the change taking place in cellular nuclei; it is more than possible that the "L.E. factor" is enzymic in nature and induces nucleoprotein denaturation and it is not impossible that disseminated lupus erythematosus is a primary disorder of nucleoprotein metabolism, possibly hormonally induced, and the major morphological changes are consequent on this. The work of Richter (1952) may also have some bearing on this disease. He has shown that the administration of nucleotides to animals undergoing immunization induces a hyperglobulinæmia without increasing the immune antibodies, and it might well be that the hyperglobulinæmia of disseminate lupus is a consequence of a disturbance of nucleoprotein metabolism.

In scleroderma and dermatomyositis there is a slow accumulation of abnormal scleroprotein in the early stages associated with an increase of depolymerized mucopolysaccharide. The protein balance is abnormal in that there appears to be an inability on the part of the cells to absorb normal metabolites and maintain chemical integrity.

In considering these two disorders as intracellular metabolic dysfunctions it is interesting to note the analogy with conditions associated with disorders of lipid metabolism—the xanthomata; in this group we have localized and generalized xanthomata and though the proximate biochemical lesion may be the same, yet the ætiological factors and resultant functional changes are very different. It may well be that we have a morphological counterpart in discoid and disseminate lupus erythematosus, circumscribed and diffuse scleroderma.

In polyarteritis nodosa the situation is very different; this is a disorder characterized by lesions in vessel walls which are essentially a cellular necrosis with protein denaturization and the symptomatic effects are consequent on the ischæmia resulting from the secondary vascular thrombosis; there is no evidence of a generalized disturbance of connective tissue although vascular lesions of an analogous type may be found in disseminate lupus erythematosus and scleroderma, but they may also be found in systemic infections and lesions, morphologically slightly different, are found in malignant hypertension. Comparable lesions can be induced experimentally in animals which have been rendered hypersensitive to certain antigens but the evidence that polyarteritis in man is, in fact, a hypersensitivity reaction is extremely tenuous. If we understood the proximate biochemical lesion inducing these vascular lesions in experimental animals and in hypertension, we might approach a little nearer to the pathogenesis and perhaps ætiology of polyarteritis nodosa; it is probable that thrombotic thrombocytopenia purpura is a related condition for all the evidence would be in favour of a primary vascular lesion.

It would seem equally, and possibly more, justifiable to class aortic cystic medial necrosis and atherosclerosis with the collagen disorders, for although it may be true that these conditions have not been acclaimed as responding to cortisone, yet the morphological evidence for a primary disorder

of connective tissue is overwhelming, and in spite of the current enthusiasm for regarding a disorder of cholesterol metabolism as the fundamental lesion, it would seem more reasonable to regard the cholesterolosis as consequential on the connective tissue change.

In discussing these conditions from the point of view of connective tissue metabolism, it should be appreciated that it is only a different approach to the same problem and yet more profit may be gained by considering the biochemical morphogenesis, of which something is known and more can be learnt, than by restricting oneself to ætiology, of which almost nothing is known.

REFERENCES

FISCHER, A. (1947) *Biol. Rev.*, **22**, 178.
HIGHBERGER, J. H., GROSS, J., and SCHMITT, F. O. (1951) *Proc. nat. Acad. Sci., Wash.*, **37**, 286.
KLEMPERER, P. (1950) *Amer. J. Path.*, **26**, 505.
——, GUEFT, B., LEE, S. L., LEUCHTENBERGER, C., and POLLISTER, A. W. (1950) *Arch. Path.*, **49**, 503.
OBERLING, C. (1943) *Rev. canad. Biol.*, **2**, 290.
PIRANI, C. L., and CATCHPOLE, H. R. (1951) *Arch. Path.*, **51**, 597.
PORTER, K. R. (1952) Josiah Macy Foundation. 2nd Conference on Connective Tissues, New York, May 24–25, 1951, New York; p. 126.
RICHTER, S. W. (1952) *J. exp. Med.*, **96**, 331.
TEILUM, G. (1952) *Ann. Rheum. Dis.*, **11**, 119.

Dr. G. B. Dowling: The care of lupus erythematosus from the time when the chronic cutaneous variety was first described by Cazenave over a hundred years ago, and its acute, or as we now say, systemic manifestations by Kaposi about twenty years later, has been until recently almost entirely in the hands of dermatologists. Beyond accurate description of its clinical features, including the predominance of the systemic disease in women they have contributed little of importance to knowledge of the disease. The latest edition of Darier's précis (1947) includes its account of lupus erythematosus in the chapter on tuberculosis, and it begins: "Although both clinically and histologically, lupus vulgaris or lupus of Willan, differs greatly from lupus erythematosus or lupus of Cazenave, the two types of lupus would appear to depend in the last analysis on the same cause, since there are serious reasons for believing that lupus erythematosus, in at least the majority of cases, is an erythemato-atrophic tuberculide." For many years, however, this, the predominant French view, was widely contested. It has long been obvious to all that the pathological anatomy of the lupus erythematosus bears not the least resemblance to that of tuberculosis. Perhaps the view most widely accepted by British dermatologists was that expressed repeatedly in this country by Barber who has held firmly to the view that the condition is a manifestation of focal infection somewhere, either streptococcal when the skin lesions are often unstable, or tuberculous when they are more often fixed and scarred. Support for this belief is found in the occasional though rare association of chronic cutaneous lupus erythematosus and tuberculous adenitis and its onset, also exceptionally, after some acute, usually naso-pharyngeal infection. Even those who have hesitated to accept any such concept have tended to regard the acute variety of the disease when it was associated with fever and grave illness, as an infective process and secondary to the cutaneous disease.

Modern knowledge of the disease begins with the discovery by Libman and Sacks (1924) of the special type of endocarditis often referred to as Libman-Sacks disease. The studies of Baehr, Klemperer and Schifrin (1935), and later of Klemperer, Pollack and Baehr (1941), added much to the picture. In addition to confirming the findings of Libman and Sacks they described in great detail the special type of pleuritis and pericarditis found in systemic lupus erythematosus, the thickening of glomerular vessels resembling wire and the curious sclerosis surrounding the central arterioles of the spleen. It was at this point that the concept of systemic lupus erythematosus as a disorder of the connective tissue as a system was formulated. The apparently unrelated alterations found in various organs in the disease, said Klemperer a few years later, had no logic, until it became apparent that they were mere local expressions of a morbid process affecting the entire collagenous system. The extracellular components of the connective tissue were primarily attacked, and the process, described as fibrinoid degeneration, was primarily and predominantly degenerative. It contrasted with the picture of inflammation, whether acute or granulomatous. Furthermore, the disease was unassociated with any evidence of bacterial infection. These studies performed in the traditional style of the great morbid anatomical school of the past, and afterwards many times confirmed, opened the gate to a new approach.

The next step was the discovery by Hargraves (1948) of a special cell found in the bone-marrow in systemic lupus erythematosus. The cell was a polymorphonuclear leucocyte containing an inclusion which stained blue with hæmatoxylin. Haserick and Bortz (1949) later showed that the same cell could be produced by adding the plasma of patients suffering from systemic lupus erythematosus to the bone-marrow of normal subjects, and further that the agent responsible for this effect was present in the gamma globulins of the patients. They referred to the formation of lupus erythematosus cells in this way as the lupus erythematosus phenomenon, and they considered it a specific diagnostic test for visceral dissemination of the disease.

Klemperer (1951) has since retracted somewhat from his definition of the pathology of systemic lupus erythematosus of 1941, because, he says, not every case has obvious connective tissue change. Additional criteria for the post-mortem diagnosis had to be found and these were forthcoming in the shape of hæmatoxylin-stained bodies—described originally by Gross (1940)—found always in large aggregates in individual endocardial vegetations and in smaller collections, or single free bodies in many organs or in the connective tissue in many sites. Cytochemical studies disclosed that these bodies contained depolymerized deoxyribose-nucleic acid, and that they were identical with the characteristic inclusions of Hargraves' cells. In other words there is a factor present in the gamma globulins of the plasma in systemic lupus erythematosus which causes the breakdown of nucleoprotein. The resultant product is seen as the inclusion bodies of Hargraves' cells and as free hæmatoxylin-stained bodies in tissues.

Klemperer has been consistently unwilling to speculate on the ætiology of the disease upon which he has done so much pioneer work. Tuberculosis he dismisses as not worth consideration. Hypersensitivity he agrees is to-day the most popular explanation of the pathogenesis of systemic lupus erythematosus. As long as fibrinoid alterations were the essential morphologic findings in systemic lupus erythematosus, supporters of the allergic hypothesis could justly claim that their opponents had no better explanation to offer. But to-day we are confronted with the fact that the lupus erythematosus cells and the hæmatoxylin-stained bodies in tissues have never been found in diseases with an allergic background. The diagnosis, however, in the living has, he says, been secured by the discovery of the Hargraves' cell in bone-marrow aspirates, while the recognition of the hæmatoxylin-stained bodies as a constant element of the histological findings in tissue has established criteria for the post-mortem diagnosis.

The old terminology in which the disease was divided into chronic, subacute and acute lupus erythematosus has now given place to a simple subdivision into systemic and cutaneous cases. The latter are subdivided for descriptive purposes into chronic cutaneous lupus erythematosus of various types, discoid or fixed, deep, localized but unstable (lupus erythematosus migrans), and less widely disseminated cutaneous cases. In the systemic disease the skin lesions are usually widespread, but they may be minimal or even absent. We cannot diagnose dissemination with certainty from the appearance of the skin alone, but we know from experience that the chronic discoid variety is unlikely to become systemic, while the fate of the unstable and the more widely disseminated cutaneous cases, those in which the face, ears, the V of the chest and sometimes the hands and forearms are involved, is uncertain.

Causal factors.—Although fundamentally the cause of lupus erythematosus is completely unknown, the background of acrocyanosis is recognized as a factor in certain cases of the cutaneous disease, and the importance of exposure to sunlight both as a determining factor in some and an aggravating factor in many of the facial cases has long been established. Some that have followed what has appeared at first to be acute sunburn have rapidly developed the systemic disease.

There is a considerable literature on the treatment of systemic lupus erythematosus with cortisone and ACTH, in almost all of which it is stated that these drugs exert a striking influence on the symptoms of the disease and promote remission in some cases. In a few reports it is claimed that the patients have been cured. Brunsting *et al.* (1951), Baehr and Soffer (1950), and others in America whose views are backed by considerable experience, say that the benefits are temporary and that little improvement in the characteristic laboratory phenomena takes place even during clinical remission. Side-effects are said to be severe when the kidneys are involved. Dr. F. T. G. Prunty has treated 3 cases at St. Thomas's Hospital, 2 of whom after temporary remission died of renal failure, while in the third treatment had to be stopped because of high venous pressure; this patient, a year later, is alive but has had systemic symptoms for ten years.

It would appear that in cases presenting the full picture of cutaneous lesions with fever, arthritis, pleuritis and pericarditis, nephritis, anæmia, thrombocytopenia and purpura, leucopenia, hyperglobulinæmia, marked rise in the sedimentation rate and the lupus erythematosus phenomenon, the prognosis is inevitably bad with or without treatment, and that visceral damage has perhaps been less severe and widespread in those patients who have derived great benefit from cortisone or ACTH, those, for example, who remit spontaneously sometimes for quite long periods. The establishment of minimal criteria of visceral dissemination would therefore be of the greatest value. It seems difficult to lay down an absolute rule as to what constitutes clinical dissemination, but the characteristic rash associated with fever without leucocytosis, a raised sedimentation rate and some degree of inversion of the normal albumin-globulin ratio seem to be constant and might be enough. In a complete review of the literature on the lupus erythematosus phenomenon, Smith (1952) states that the Hargraves' cell can be found in almost but not quite all cases of the systemic disease.

Dermatologists are naturally chiefly concerned with the treatment of purely cutaneous lupus erythematosus, particularly the common discoid variety, a condition which has no effect whatever upon physical health but is often grossly disfiguring. Most of the remedies that have been in common use for years, such as quinine, gold, bismuth, sulphonamides and organic arsenical compounds have

sometimes produced some change for the better and occasionally for the worse. It is generally admitted in fact that treatment is thoroughly unsatisfactory. Recently, Page (1951) noted by accident, he says, in treating a patient who had discoid lupus erythematosus, for some other condition with Mepacrine, that the lupus erythematosus cleared up. He therefore proceeded with the co-operation of Dr. F. Ray Bettley to treat 17 others, including 2 with arthritis and 1 with systemic lupus erythematosus. Of these cases the result of treatment in 9 is described as excellent and in 6 good; in 2 slight improvement was noted and in 1 no change occurred. The systemic case had a stormy passage but appeared to be well in four months. Those with arthritis did well, the joint symptoms disappearing with improvement in the eruption. From personal experience I would rate this remedy a considerable advance upon its predecessors. The patients have to put up with some degree of the muddy yellow colour in the skin that the drug produces, but they seem to find this far less objectionable than the lupus. Complete resolution of a scarred discoid lesion is probably unusual, but in quite a high proportion of cases about 75% of improvement seems to be achieved. We have no idea of how Mepacrine can act.

Scleroderma and dermatomyositis.—The cutaneous lesions of dermatomyositis often bear a strong clinical resemblance to those of lupus erythematosus, particularly those of the hands and fingers. There are differences, the most important being an almost constant œdematous swelling of the malar area in the early stages of dermatomyositis and a regular arrangement of the lupus erythematosus-like change on the hands in bands along the fingers and over the metacarpal bones. Here the resemblance ends. The disease is almost evenly distributed between the two sexes, it can occur at any age, serositis does not occur unless it is due to some infective cause, renal function is not impaired, there is no inversion of the normal albumin-globulin ratio; and the Hargraves' cell is not found in the disease. Creatinuria may occur in both conditions but it is constant in dermatomyositis and often absent in systemic lupus erythematosus. Leucopenia has been occasionally reported. Muscular weakness is the principal symptom and in the most severe cases it produces symptoms resembling those of bulbar palsy in addition to weakness of the skeletal muscles. Although often accompanied by fever especially in its early phase it is, like lupus erythematosus, a non-bacterial disease. It may pursue a fulminating course terminating with death within weeks or it may smoulder for many years without remission. A proportion recover.

Langmead (1923) first identified dermatomyositis with the type of scleroderma known as diffuse or progressive symmetrical scleroderma with sclerodactylia; though little notice was taken of his paper which was based chiefly on literature, this view has by degrees gained wide though not universal acceptance. Looking at a case of fulminating dermatomyositis side by side with one of scleroderma with sclerodactylia and Raynaud's phenomenon it is difficult to believe that the two could be related in any way. However, all transitional grades are met with, and to some cases either term might be applied equally well. Such a case was shown by Dr. H. A. Treble in December 1951. It was that of a woman who presented the skin changes of dermatomyositis on the hands, arms and face and of scleroderma on the body. The points in favour of the unity of the two conditions are these: The distribution of the cutaneous change is precisely the same in both; general myasthenia is often as well marked in scleroderma as in dermatomyositis. Raynaud's phenomenon occurs in both though with far greater frequency in scleroderma than in dermatomyositis. Calcinosis occurs in both diseases. In chronic dermatomyositis sclerosis develops gradually in affected parts of the skin and the well-known facial mask of scleroderma sometimes follows the preliminary phase of œdema and erythema of dermatomyositis. The histological appearance of the skin in such cases is that of scleroderma. On the other hand some lesions that are not met with in the acute phase of dermatomyositis occur with some frequency in scleroderma and, in intermediate cases, especially dysphagia due to what appears radiologically to be constriction of the lower end of the œsophagus and similar constrictions elsewhere along the course of the alimentary canal. The well-known interstitial pulmonary fibrosis and the interstitial sclerosis and fibrosis of the connective tissue of the heart, are also found almost exclusively in scleroderma. Limited varieties of the process are quite common and have acquired separate names, especially acrosclerosis and what is usually termed the Thibierge-Weissenbach syndrome. There is no point in the use of the term acrosclerosis except as a synonym for progressive symmetrical scleroderma, but the Thibierge-Weissenbach syndrome is interesting because of the frequency with which it is associated with dysphagia. It consists of Raynaud's phenomenon with more or less scleroderma of the fingers, sometimes very little, calcinosis both of the fingers and of other parts in which there is no other skin change; and invariably the characteristic sclerodermatous mask with telangiectasis of the rigid facial skin. Interstitial diffuse pulmonary fibrosis also occurs occasionally in this limited variety of the disease.

The pathology of dermatomyositis and diffuse scleroderma has been studied by many observers. A very complete post-mortem analysis of a case diagnosed dermatomyositis by Talbott and others (1939) but in which the skin change according to the description was that of scleroderma, revealed for the first time widespread change in small arterioles throughout the body, but especially in the kidneys where a special type of endarteritis was discovered in vessels supplying areas of cortical degeneration. They pointed out that in spite of what appeared anatomically to be severe renal damage, function had not been impaired at any time. Similar vascular change was found in small vessels in many other

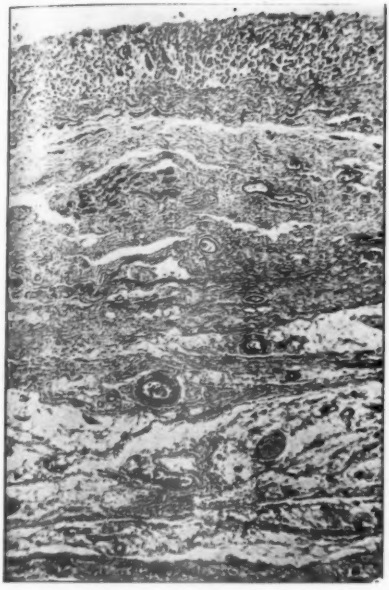


FIG. 1.—Section through wall of œsophagus about 1 in. above the cardiac orifice, showing gastric type of mucosa and almost complete disappearance of the muscle coat. There is a little fibrous tissue replacement but no scar formation. The muscularis mucosæ is intact. × low power.

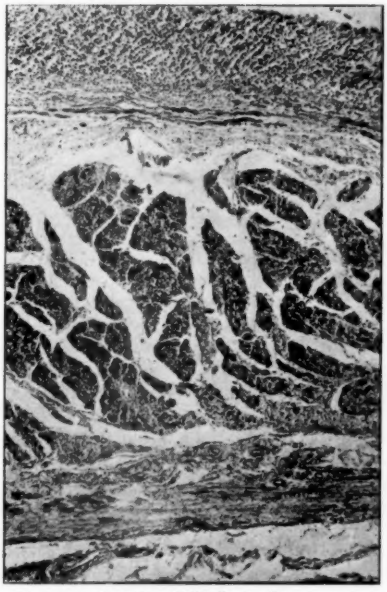


FIG. 2.—Another field from the same section about ½ in. above Fig. 1, for comparison. It shows an intact transverse muscular coat, while the longitudinal fibres are partly damaged. × low power.

organs. Goetz (1945) in a detailed post-mortem study of a case which had been steadily progressive for many years, confirmed these findings in the small vessels.

In a case of scleroderma with gross asthenia and dysphagia who died at St. Thomas's Hospital, Dr. Ian Whimster reported that the principal œsophageal change consisted of gross atrophy of the external muscular coats both longitudinal and transverse (Figs. 1 and 2). Similar degeneration has been described by Goetz both at the lower end of the œsophagus and at other points of constriction in the colon. In more than one rapidly fatal case of acute dermatomyositis under my care no abnormality has been found in small arteries in the kidneys and other organs, a fact which suggests that vascular changes may develop slowly. Goetz who readily accepts the identity of progressive scleroderma with dermatomyositis thinks that the term scleroderma should be abandoned. He says that it is a systemic disease, neither solely nor primarily involving the skin, and that the term should be replaced by one which describes more accurately the true state of affairs; as the term sclerosis is already in use, he suggests the title Progressive Systemic Sclerosis.

I have under observation a case of chronic dermatomyositis of the intermediate type; he has Raynaud's symptoms, gross myasthenia, some sclerosis in bands over the digits and metacarpal bones with little limitation of movement and the facial mask of progressive scleroderma. Skin from this case has been subjected by Dr. R. Reed at Dr. R. H. Seville's suggestion to examination by the electron microscope and compared with that of a case of dense scleroderma. The same picture is seen in both. The collagen fibres appear to be practically normal and a certain amount of amorphous material, present in normal connective tissue, but in far lesser quantity, is seen in the preparations. Digestion with weak trypsin removes the amorphous material and leaves the fibres intact. These findings are thought to indicate that while the fibres are perhaps normal, the ground substance is altered. Musso and Seville are working on the same problem by histological methods at the Institute of Dermatology and hope by digestion to remove the ground substance and reveal fibres of normal size and shape.

There are a few published reports, both favourable and discouraging on the treatment of dermatomyositis and progressive scleroderma with cortisone and ACTH. 3 cases of dermatomyositis, all of considerable severity, have been treated by Dr. Prunty at St. Thomas's Hospital without material benefit.

Finally, there is an interesting clinical observation to which Forman (1952) has drawn the attention of dermatologists. A number of cases of dermatomyositis have been found to be associated with carcinoma in various organs. I have personally seen 2 within the last six months, both with carcinoma of the ovary. There are published records of about 20 such cases, most of which are reviewed by Brunner and Lobraiso (1951). In a few it is stated that removal of the growth has been followed by remission of dermatomyositis. In the absence of any knowledge of the pathogenesis or ætiology of dermatomyositis it is useless to speculate on the significance of this observation.

BIBLIOGRAPHY

BAEHR, G., KLEMPERER, P., and SCHIFRIN, A. (1935) *Trans. Ass. Amer. Phys.*, **50,** 139.

——, and SOFFER, I. J. (1950) *Bull. N.Y. Acad. Med.*, **26,** 229.

BRUNNER, M. T., and LOBRAISO, R. V. (1951) *Ann. intern. Med.*, **34,** 1269.

BRUNSTING, L. A., SLOCUMB, C. H., and DIDCOUT, J. W. (1951) *Arch. Derm. Syph. Chicago*, **63,** 29.

DARIER, J., CIVATTE, A., and TZANCK, A. (1947) Précis de Dermatologie. 5th Edit. Paris: p. 826.

FORMAN, L. (1952) *Brit. J. Derm.*, **64,** 65.

GOETZ, R. H. (1945) *Clin. Proc., Cape Town*, **4,** 337.

GROSS, L. (1940) *Amer. J. Path.*, **16,** 375.

HARGRAVES, M. M., RICHMOND, H., and MORTON, R. (1948) *Proc. Mayo Clin.*, **23,** 25.

HASERICK, J. R., and BORTZ, D. W. (1949) *J. invest. Derm.*, **13,** 47.

KLEMPERER, P. (1951) In Soc. Belge de Dermat et de Syph. Livre Jubilaire, 1900–1951. Imp. Met et Scientifique, Brussels: p. 40.

——, POLLACK, A. D., and BAEHR, G. (1941) *Arch. Path.*, **32,** 569.

LANGMEAD, F. (1923) *Arch. Pediat.*, **40,** 112.

LIBMAN, E., and SACKS, B. (1924) *Arch. intern. Med.*, **33,** 701.

PAGE, F. (1951) *Lancet*, ii, 755.

SMITH, P. A. J. (1952) *Brit. J. Derm.*, **64,** 10.

TALBOTT, J. H., GALE, E. A., CONSULAZIO, W. V., and COOMBS, F. S. (1939) *Arch. intern. Med.*, **63,** 476.

TREBLE, H. A. (1952) *Brit. J. Derm.* **64,** 291.

Section of Laryngology with Section of Otology

JOINT SUMMER MEETING WITH THE NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY HELD AT MANCHESTER ROYAL INFIRMARY

LARYNGOLOGICAL SESSION

[*June* 14, 1952]

Chairman—F. C. W. CAPPS, F.R.C.S. (President of the Section of Laryngology)

Bilateral Abductor Paralysis

Arytenoidectomy for Bilateral Abductor Paralysis—Extralaryngeal Approach

By DE GRAAF WOODMAN, M.D.

THE complication of injury to both recurrent laryngeal nerves during the course of thyroid surgery is relatively rare. When it does occur, it generally takes one of two forms of paralysis. The commoner of the two is that of the paramedian or so-called "cadaveric" position with the cords in a relatively flaccid state. In this type of paralysis air can generally flutter back and forth through the glottic chink, and in some cases patients can manage to get along for years in a state of semi-invalidism as long as they make no great exertion, but they remain handicapped for life. The other form of paralysis is that of the spastic adductor state in which the cords are brought tightly together and little or no air passes. In this type an immediate airway via a tracheotomy or intubation tube is necessary to prevent asphyxia.

When a flaccid paralysis occurs, the problem arises as to what to do as far as airway is concerned. We feel it is better to do an early tracheotomy rather than delay and risk chronic dyspnœa and its attendant ills. Murtagh *et al.* (1950) have shown that once all dyspnœa is overcome, the patient's whole condition improves. There is less chance of chronic respiratory and myocardial damage.

If there is no sign of return of function of either of the vocal cords within six months, then is the time to consider plastic correction of the vocal cord paralysis.

Review of the literature for over one hundred years on bilateral abductor paralysis surgery shows that the first to carry on experimental work was Professor Gunther of the Hanover Veterinary School in 1834. Williams (1907) performed a ventrical stripping operation successfully. Hobday (1911) reported 250 cases and in 1921 reported on over 2,000 cases.

In humans up until a few years ago the placement of a tracheotomy tube was the only certain method of relief. Mr. E. Musgrave Woodman, in 1924, reported the first adaptation of cordopexy to human laryngeal surgery and about the same period the works of I. Moore and Wilfred Trotter appeared. Many forms of intralaryngeal surgery and laryngofissure approaches were tried and many of these resulted in further scarring of the glottis and an increase in the stenosis. There were very few successes.

In 1939 Brian King had the notion that he could solve the problem by attaching the omohyoid muscle to the arytenoid cartilage and by this manœuvre help pull the glottic chink laterally and thus obtain sufficient airway to permit removal of the tracheotomy tube. This extralaryngeal approach rekindled interest inasmuch as it did not lead to further scarring and stenosis of the glottic chink. Kelly (1941), of New York City, felt that arytenoidectomy was preferable. Removing the arytenoid cartilage itself gives a 3 mm. space. However, his technique was difficult to copy as he worked through a 1 centimetre aperture in the lateral thyroid cartilage.

Combining features of both King and Kelly we have developed a technique at the Columbia Presbyterian Medical Center in New York which has permitted arytenoidectomy together with lateralization of the cord. Lateralization is essential, as the space obtained by arytenoidectomy alone is not sufficient to relieve all dyspnœa. This technique has been carried out at the Center on about 40 cases since 1944 and we have had reports from other parts of the world on over two hundred cases in which the same procedure has been used with success.

When the operated cord is lateralized and anchored it becomes fixed. This forces the unoperated cord to adduct past the mid-line in order properly to phonate. The Speech and Phonology Sections of our Department of Otolaryngology have rehabilitated these voices so that they can carry on without difficulty (Woodman and Pollock, 1950).

Procedure.—If a preliminary tracheotomy has not been done, the patient is prepared under local anæsthesia, with the placement of an intratracheal tube (under guidance of the laryngoscope). The tracheotomy may then be performed with local anæsthesia, or intravenous anæsthesia may be started and the tracheotomy done with the patient under general anæsthesia.

(1) After tracheotomy an incision is made along the anterior border of the sternocleidomastoid muscle at the level of the upper edge of the thyroid cartilage and carried down to the level of the cricoid cartilage.

(2) The sternocleidomastoid muscle is retracted, exposing the posterior edge of the lateral thyroid cartilage (Fig. 1) with the thyrohyoid muscle attached anterior to its posterior edge and the inferior pharyngeal constrictor muscle attached to its posterior edge and to the inferior cornu. The attachment of the inferior cornu to the cricoid cartilage is a key landmark.

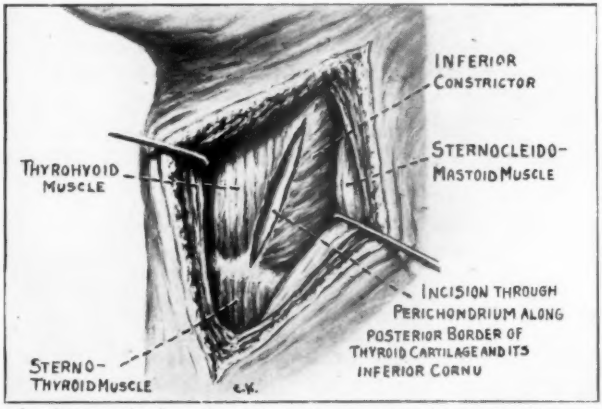


FIG. 1.—An incision has been made along the posterior border of the lateral thyroid cartilage and the inferior cornu down to and through the perichondrium.

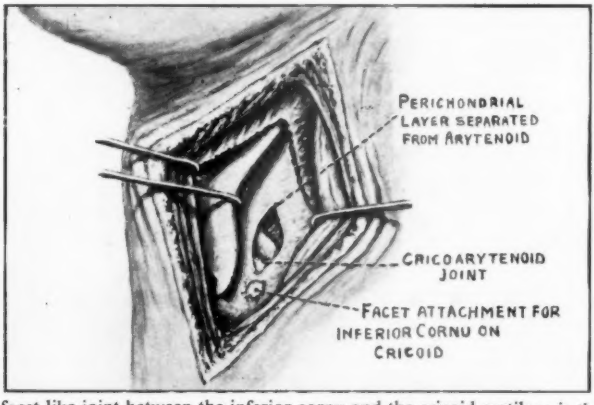


FIG. 2.—The facet-like joint between the inferior cornu and the cricoid cartilage is then separated.

(3) A vertical incision is made along the posterior edge of the lateral thyroid cartilage and the inferior cornu down to and through the perichondrium. The inferior constrictor muscle is separated posteriorly; the cartilage is hugged closely, and the perichondrium is elevated around the posterior edge on to its mesial side sufficiently to free it of attachments to the inferior constrictor muscle. The facet-like joint between the inferior cornu and the cricoid cartilage is then separated. The incision is carried through the perichondrium on the lateral wall of the cricoid cartilage and continued vertically upward (Fig. 2) until the subperichondrial dissection of the arytenoid cartilage has been accomplished. When dissection of this structure has been done, the joint is disarticulated. A traction ligature is then placed around the middle portion of the arytenoid cartilage (Fig. 3), and the cartilage is rotated laterally.

With the aid of this traction ligature, the vocal process can be well exposed. At this point the intratracheal tube is withdrawn before proceeding further. A curved atraumatic needle with 0 chromic surgical gut is passed around the vocal process, care being taken to keep it in the submucosa and to pass it through and to include some of the fibres of the vocalis and the thyro-arytenoid muscles. After placement of this suture, all the arytenoid cartilage is removed except the non-articular part associated with the vocal process. The cord suture is then drawn laterally and tied around the inferior cornu of the thyroid cartilage (Fig. 4); and this, in turn, may be reinforced by anchoring the suture to the anterior edge of the sternocleidomastoid muscle. If the attachment of the cord to the inferior cornu should cause too much lowering of its horizontal plane, this fault may be overcome by the optional attachment of a 0·32 cm. drillhole anterior to the posterior edge of the thyroid cartilage at the desired level.

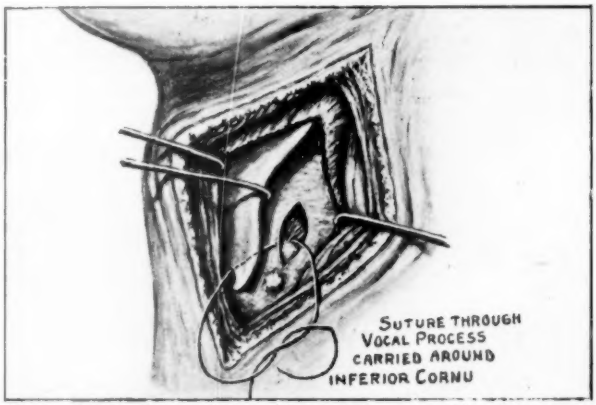


FIG. 3.—A traction ligature is placed around the midpart of the arytenoid and the cartilage rotated laterally.

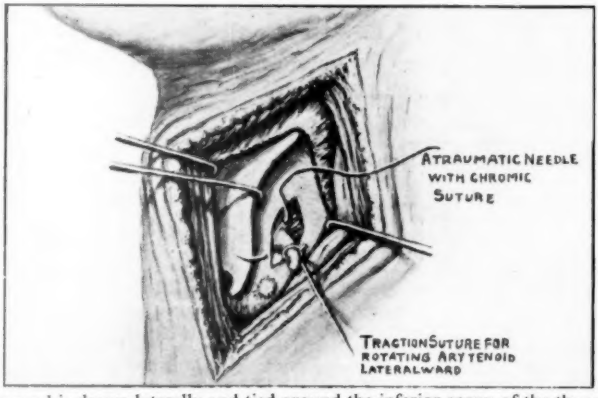


FIG. 4.—The cord is drawn laterally and tied around the inferior cornu of the thyroid cartilage.

Before the wound is closed the larynx is inspected with the laryngoscope and careful note made of the position of the cord.

Closure is made by bringing the inferior constrictor muscle back into place with a few separate sutures. Interrupted sutures close the skin, a Penrose drain being left in the lower end of the wound and removed on the fourth post-operative day.

[The 4 figures illustrating this paper are reproduced from *Ann. Otol. Rhin. Laryng.*, 1948, **57**, 695, by permission.]

BIBLIOGRAPHY

HOBDAY, F. (1911) *Proc. R. Soc. Med.*, **4**, Sect. Laryng., p. 87.
KELLY, J. D. (1941) *Arch. Otolaryng., Chicago*, **33**, 293.
KING, B. T. (1939*a*) *J. Amer. med. Ass.*, **112**, 814.
—— (1939*b*) *Trans. Amer. laryng. Ass.*, **61**, 264.
MOORE, I. (1924) *Vet. J.*, **80**, 228.
MURTAGH, J. A., MOISTER, F. C., and MILNE, J. (1950) *Laryngoscope, St. Louis*, **60**, 330.
WILLIAMS, W. L. (1907) *Amer. vet. Rev.*, **32**, 333.
WOODMAN, DE G. (1946) *Arch. Otolaryng., Chicago*, **43**, 64.
—— (1948) *Ann. Otol. Rhin. Laryng.*, **57**, 695.
—— (1949) *Arch. Otolaryng., Chicago*, **50**, 91.
——, and POLLOCK, D. (1950) *Laryngoscope, St. Louis*, **60**, 832.

The President said that he himself had operated on five cases and had found that the insertion of the suture around the vocal process was the difficulty. He wondered if this was always necessary, especially as it took sometimes a long time and there was a risk of damaging the lumen of the larynx. Was not the arytenoidectomy the crux of the business? That and that only was done in some Clinics in America.

In one of his five cases he (the President) had thought that there was so little disturbance that he had omitted the tracheotomy. All went well in the end but his house surgeon had had a very anxious week.

Professor F. C. Ormerod had performed a number of operations by the King method but he found Dr. Woodman's technique easier and the results better. He now employed this technique as a routine and had good results. The breathing was much better and the patient able to lead a normal life, while the voice was only lowered a little in tone. He had recently seen some patients abroad in whom two sutures had been passed through the vocal cord and out through the thyroid ala, and tied subcutaneously. These provided very good abduction and airway but the voice was completely lost.

Mr. R. D. Owen said that while in New York he also had the privilege of seeing the results of Dr. Woodman's operation.

Even in expert hands the external approach to the arytenoid cartilage was not an easy one. There was much to be said in favour of Thornell's technique of the direct approach with suspension laryngoscopy, but in Mr. Owen's experience the thyro-fissure approach was much more simple.

When the larynx had been split open, the first essential step was to produce ischæmia of the mucosa over the arytenoid cartilage to be removed. A curved incision was made, starting at the level of the cuneiform cartilage, and brought forward towards the vocal process. A submucosal dissection of the arytenoid was easily carried out, and the field kept clear with a small dissecting sucker. After the removal of the cartilage, two or three touches with a small coagulating diathermy button were made within the cavity. This helped to increase the degree of fibrosis. The cut mucosal edges were brought together with one or two fine catgut sutures, and then the larynx was closed up. The tracheotomy tube was removed in seven to ten days.

Mr. Owen said that he was well satisfied with the 5 or 6 mm. abduction of the vocal cord as the result of this method, and, further, the removal of the arytenoid cartilage appeared to be all that was necessary, without troubling about anchoring the vocal process. Finally, the voice was surprisingly good.

Mr. G. E. Archer had been interested in this subject for some years and had operated upon a number of cases. He had performed what was essentially King's operation with slight modifications in order to fix the arytenoid cartilage in a more lateral and abducted position, without attempting any muscular plastic procedure.

He had removed the arytenoid cartilage in only one instance and this inadvertently, as the sutures had cut through the cartilage and broken it into fragments. This had resulted in a somewhat floppy cord.

The noise the man made in his sleep was very trying to his wife. The modified King's operation was subsequently performed on the opposite side with a good result.

Mr. Archer said Dr. Woodman had emphasized the importance of getting rotation of the arytenoid in these cases. As described in this (King's) operation the suture fixing the arytenoid is put round the posterior border of the thyroid ala. It would seem that this was not the best place to put it. The method adopted had been to make two small perforations through the wing of the thyroid cartilage—one above the other—3/16 in. apart and 3/8 in. from the posterior border. This had been done with a fairly large hypodermic needle carrying the suture material threaded through the needle, so that the suture material was picked up on the inner surface as the needle was withdrawn. The material was then passed round the vocal process keeping under the mucosa so that when the suture was tied on the outer surface of the thyroid ala the vocal process was drawn forward to the site of the perforations on the inner surface of the thyroid ala. In this way the arytenoid having been previously freed from its muscular and ligamentous attachments was drawn laterally and abducted.

The essential point necessary to retain an efficient voice was to fix the cord at the correct level. A displacement upwards or downwards will ruin the volume of the voice.

Dr. J. C. McFarland had found it helpful, when removing the arytenoid cartilages, to wear operating spectacles giving slight magnification. The insertion of the traction suture was facilitated by the use of Irwin Moore's septum needle. The method advocated of passing the suture underneath the inferior cornu *did* tend to pull the vocal cord downwards and the method of passing the suture through the thyroid cartilage was to be recommended.

Mr. E. D. D. Davis's experience of this operation was limited to a number of dissections of post-mortem larynges, 5 of which were exhibited. It might be difficult to expose the arytenoid cartilage.

The rallying points were the posterior edge and inferior cornu of the ala of the thyroid cartilage. The muscular process of the arytenoid and the joint between it and the cricoid were defined. The arytenoid cartilage was dissected free and a retaining suture slipped round the cartilage to act as a tractor and then with a special fine curved needle a ligature encircled the vocal process. The arytenoid without the vocal process was excised.

Mr. Davis had seen 5 women with double abductor paralysis following thyroidectomy. The chief complaints were "roaring" when asleep—which disturbed the household—and shortness of breath on exertion. 4 refused to have tracheotomy. One has worn a tracheotomy tube for fifty years and recently applied for a new tube. Mr. L. Colledge did an anastomosis of the right recurrent laryngeal and the phrenic nerves for one patient with no improvement. This patient's breathing was so embarrassed during pregnancy that an abortion was performed.

Mr. William McKenzie said he had a patient who was a plasterer and who had a great deal of difficulty in doing his work, and he performed the operation as had been described. The arytenoid broke; he put a ligature round it and tied it, and when he looked at it afterwards the cord was well abducted and he was very pleased. The patient's general condition changed quite obviously and he went back to work. Later he saw the patient again, and the cord had gone back to the same position as before the operation.

Would it be wiser for an apprentice to leave the tracheal tube in for perhaps two or three months to avoid such an occurrence. As far as he could see he had done everything he should and in spite of this the cord had gone back into the same position.

Mr. V. E. Negus said that with a suitable tracheostomy his patients were so comfortable that they did not wish to have any further operation. The patients were told that preliminary tracheostomy was desirable and that a displacement operation could be performed if they were dissatisfied with the tube. So far none had elected to have this done.

He was not quite clear whether Dr. Woodman preferred to perform tracheostomy at the time of the displacement operation, or to carry it out some days before.

Mr. Negus considered that the advantages of a satisfactory tracheostomy with a properly made respiratory valve were that the patient had free respiration and a clear voice; he had yet to be converted to the view that the freedom of respiration and the clearness of voice were as good in a displacement operation as with a suitably placed and properly designed cannula. It seemed that much of the prejudice against tubes was because of their wrong design.

He was sure that the information given by Dr. Woodman at the meeting would be of much value in undertaking the procedure.

Mr. Neville Young asked how long a tracheal tube should stay in after operation. He believed that its early removal resulted in the best vocal result; and had been able to leave it out within a month in each of his cases.

Mr. M. Spencer Harrison said that in the provinces there might be more of these cases than in London. In his earlier cases a tracheostomy was left after operation but latterly a large polythene endotracheal tube had been left in the larynx post-operatively for up to four days. This helped to hold the cord laterally and to lessen the œdema. It was removed in the theatre where the airway could rapidly be re-established if trouble arose; but none had occurred and the results, particularly as regards airway and voice, had been very satisfactory.

Mr. Myles L. Formby said that in a series of some 10 or 12 cases on which he had performed the Woodman operation, only once did he not perform a tracheostomy and this case ended fatally.

Dr. Woodman, in answer to the President about whether it is worth while putting the suture around the vocal process, said that while scar tissue might be sufficient to obtain a result it was not reliable enough to depend upon, therefore it was better to make every effort to get the suture around the vocal process and to include in that suture some of the vocalis muscle. It was therefore important to have a good atraumatic chromic suture for this part of the procedure. He had used and recommended the Davis and Geck atraumatic single O Chromic suture with a sharp needle.

In answer to Mr. Ormerod he agreed it was well not to try to grasp the arytenoid cartilage as it invariably cracked or fractured. He now often steadied it against the intratrachial tube with the tip of a suction tube. In regard to having seen and done cases of bilateral abductor paralysis secondary to other conditions besides post-thyroid surgery, he had done cases secondary to lues, syringomyelia, a case secondary to radiation therapy for carcinoma of the neck and a case following typhus fever. The latter two cases had arytenoids which had completely lost their structure and normal outline and were merely rubbery fibrous bands. These cartilaginous changes were apparently secondary to the irradiation and the typhus fever.

Mr. Owen's comments on his recent success with a laryngofissure type of approach and arytenoidectomy endolaryngeally was somewhat similar to that described by Loré; however, while this may well have proven satisfactory in his hands, when scarring occurred within the larynx an increase in the stenosis resulted and past experience had often proven this approach more prone to this complication.

In answer to Mr. Archer he had had no experience such as he had mentioned with a resulting floppy cord. This probably resulted from the suture not being placed properly or coming loose after being placed. He now always used two sutures for added security. He was interested to hear that Mr. Archer, too, had had difficulty with the cartilage splitting on attempts to manipulate it or pass a suture through it.

With regard to Mr. Davis's suggestion that the muscular process of the arytenoid was a good landmark to start with in dissecting out the arytenoid one should remember that the position of the arytenoid could vary considerably, depending on the size of the intratracheal tube which had been placed and the size of the larynx itself. These factors might disturb the normal position and relationship of the arytenoid and give it a different slant. If, however, one searched for and found the prominent muscular process, that was the best point from which to start the dissection.

Mr. McKenzie's case, probably another in which the suture came loose, emphasized the value of placing two sutures. He had had no primary failures but in cases which had had both cords operated upon without success, he had only been able to decannulate 2 out of 5 of such cases. He would not recommend leaving an intratracheal tube in for any period over twenty-four hours, as this presented an additional risk of trauma to the cords and possibly resulting granuloma formation.

In answer to Mr. Negus's question they much preferred to have the tracheotomy done previously, preferably a week or ten days before the plastic procedure though in about 20% of their cases they had performed a one-stage operation. These cases were not easy to do and there had been moments during the operation when he had felt that perhaps it would have been better to have followed Mr. Negus's more conservative policy and have resorted to a valve type tracheotomy tube. However the effort had usually proven well worth while by the end-result.

In answer to Mr. Young there was no reason for hurrying the removal of the tracheotomy tube. Their average was twenty-six days on the first 23 cases they had reported. More recently they had been getting them out in about fifteen days. They removed them only after full corking of the tube for four days, with vigorous exercise and work. When there was no handicap in breathing under those conditions, then they removed the tube.

Mr. Spencer Harrison's experience with the intratracheal tubes being left in place for four days and then removed was new to Dr. Woodman, who felt that the œdema after only four days would hardly make it safe to do this.

He was interested in Mr. Myles Formby's mention of the sequel to the case in which no tracheotomy tube had been placed, as this type of operative work offered too much of a hazard along this line to risk not using a tube in all cases. They had tried not using a tube on their first case in 1944 and the same night they were forced to do a tracheotomy as a life-saving measure.

Mixed Salivary Tumours of the Upper Respiratory Tract

By Professor VICTOR LAMBERT, F.R.C.S.

THE speaker first stressed the complicated nomenclature used to describe the tumours of this group. The older pathologists had variously suggested that the tumours were: (*a*) pure mesenchymal tumours: (*b*) tumours of mixed origin; and (*c*) that they were wholly epithelial in origin. This last view is the commonly accepted one to-day, although the actual nature of their epithelial origin has not been accurately defined. It is variously thought that the origin of the tumours may be from adult glandular tissue, non-adult tissue, or early non-differentiated epithelium of membranous origin.

The mixed salivary tumour, therefore, the Speaker accepted as being an epithelial tumour which as a result of the epithelial elements grouping around a central lumen, should be regarded as adenomatous in type.

The adenomatous mass of the tumour appears to excite a reaction in the mesenchymal elements, this reaction resulting in the formation of a myxomatous or jelly-like matrix, in many cases closely resembling cartilage. Some pathologists actually regard the change as a true cartilaginous metaplasia.

The mixed adenomata being found most commonly in the larger salivary glands—particularly in the parotid, less frequently in the submaxillary and sublingual glands, and as clinical rarities in the lacrimal gland—do from time to time occur in the palate, nasal passages, tongue, larynx and trachea.

The Speaker accepted Willis's contention "that the mixed tumours are adenomata and lowly malignant adenocarcinomata with a wide range of structure and behaviour, and that they merge insensibly with the simple adenoma on the one hand, and with the frankly anaplastic carcinomas on the other".

Table I is taken from the records of the Christie Cancer Hospital and Holt Radium Institute. In considering the figures it should be remembered that they are taken from a Centre which deals predominantly with malignant disease, and the figures therefore should not be considered as truly representative of the comparative incidence of the simple and malignant variety of the tumours under consideration.

TABLE I.—AN ANALYSIS OF CASES OF MIXED SALIVARY TUMOURS OCCURRING IN SITES OTHER THAN SALIVARY GLANDS (39 CASES)

Females 23. Males 16.

Age groups	Simple	Malignant
20–30	—	2
30–40	2	5
40–50	4	5
50–60	2	7
60–70	2	7
70 plus	—	3
Totals	10	29

Sites	
Tongue	4
Soft palate	12
Hard palate	13
Floor of mouth	2
Neck—? pharynx	1
Nasal passages	5
Cheek	2
	39

Malignant	
Females	16
Males	13
	29

17 died of malignancy, mostly within two years.

Brief case histories with slides of the primary tumours, and in some cases metastatic deposits in neck glands, were presented.

From the survey of the series, the following deductions were made: that the incidence of malignancy in this type of tumour in unusual sites tended to be commoner than in the corresponding tumour in a salivary gland; and that the degree of malignancy in many of these tumours was difficult to assess, both clinically and from their histology.

The tumours forming the series under consideration were treated, some by surgery, some by surgery plus irradiation, and some by irradiation alone. It would seem that the slowly growing tumours were more suitable for surgery or surgery plus irradiation, and the more rapidly growing tumours were probably best treated by irradiation alone. A doubt was also expressed as to whether the tumour which started as a simple tumour of this type ever really became malignant, and that the malignant type was malignant from the beginning.

The pitfalls of unrepresentative biopsies were also stressed.

The speaker wished to acknowledge the help of Dr. H. Russell, the pathologist of the Christie Cancer Hospital and Holt Radium Institute, and that of all his colleagues.

The President mentioned that he had seen several such cases, the largest being about 5 in. long arising from the palate and presenting in the submaxillary region. It caused great difficulty in breathing, speaking and feeding. His surgical colleague Mr. R. S. Corbett had, on his advice, removed it and it had shelled out with great ease. He had also had an example of one on the hard palate, a localized swelling which Dr. N. S. Finzi had treated with radium. Twelve years later it had become epitheliomatous.

Mrs. Florence Cavanagh said she had seen 3 cases in children. The first case was a boy of 5 whose tonsils and adenoids had been removed a few weeks previously. He returned to hospital because there was a small mass of tissue hanging behind the uvula. This looked like an adenoid tag and was removed. It felt rather firmer than was expected and section showed a mixed salivary tumour. The boy was seen regularly for several years but there was no recurrence.

The second case was in a child whose tonsils and adenoids were being removed. The tonsils were regarded as tuberculous and were sent to the pathologist. No tuberculosis was found but one tonsil contained a mixed salivary tumour. There has been no recurrence.

The third case was that of a child with multiple congenital abnormalities. There was a cleft palate and the tongue appeared to be in three parts: the two lateral pieces looked like normal tongue tissue, the third portion was smaller and stood up in the mid-line posteriorly. It looked like a small red cherry and was thought to be lingual thyroid. The cleft in the palate was not obvious at first as a large tumour filled in the gap between the two halves. This mass was 2 in. long antero-posteriorly and 1½ in. wide. It appeared to have a covering of skin on which fine hairs could be seen and resembled a dermoid. The posterior end looked like normal adenoid tissue. The anterior end was firm and fleshy. Sections were taken from the cherry red knob of tongue, the adenoidal end of the nasopharyngeal mass and also the anterior free portion of this mass. All three sections showed mixed salivary tumour—despite the gross difference in macroscopical appearance.

Mr. E. D. D. Davis said he had the notes and microscopic slides of 21 cases of mixed salivary gland tumours. 7 were malignant and recurred after excision. The benign encapsuled tumours were ubiquitous and were found in the face, mouth, palate, pharynx and neck.

The structure varied considerably and different types had been described. (1) The soft mucous gland type in which a mucilaginous substance predominated and the stroma was fine and abundant; (2) the hard fibrous nodular tumour with a marked fibrous stroma; (3) the pale myxomatous tumour resembling a lipoma; and lastly (4) the epithelial tumour, in which the epithelial cells predominated and were arranged in groups. The epithelial tumour was considered by most pathologists to be malignant.

There was considerable difficulty in distinguishing the benign tumour from the malignant by microscopic section alone.

When the benign tumour was excised with the capsule complete, there was no recurrence for twenty, sixteen, and in many for more than five years. Complete excision was the most successful treatment and radiotherapy was undesirable.

The malignant tumour occurred in older people and was painful. It was not encapsuled and circumscribed. It involved the skin and superficial tissues early. As a rule the benign tumour could be distinguished easily at an operation and by clinical examination.

A very few apparently encapsuled tumours had been enucleated and a recurrence had appeared within two years and widespread dissemination has been seen. In this type the epithelial cells predominated.

Mr. R. R. Simpson asked whether Professor Lambert thought the cylindromas were of the same family as the mixed salivary tumours.

Mr. Norman Appleton had recently had a case of a tracheal swelling which proved to be a mixed salivary tumour. Local removal was performed by the external route, but rapid recurrence took place. This case must have been similar to Mr. Simpson's.

Mr. J. H. Otty had had two similar cases in the larynx. The first was that of a woman, 30 years of age, who, for many years, had been treated as a case of pulmonary tuberculosis because of repeated hæmoptysis. There was a smooth tumour in the subglottic region; the vocal cords were healthy and their movements good. X-ray examination showed the tumour to be almost completely obliterating the airway. A biopsy suggested that it was of the nature of a bronchial adenoma. In view of the poor airway total laryngectomy was done. The

patient made a good recovery, and is still alive and well. A specimen was further examined in the Middlesex Hospital where it was reported that it was a mixed salivary tumour.

A year ago he saw a lady of 75 years of age with a smooth tumour involving the left false cord. A biopsy from this suggested it to be a salivary tumour. The tumour was increasing in size and it was removed by laryngofissure. The diagnosis was further confirmed. She, too, has made a good recovery and is alive and well.

Professor Lambert replying to Mr. R. R. Simpson said that he had only seen 2 cases of malignancy in the trachea, and only 2 cases of mixed adenoma in the trachea.

He also said that in his view the cylindroma was part of the same family of tumours.

The speaker had not seen any of these tumours in children, and expressed his surprise that the tumours did not occur more frequently in the tonsillar region in children, because a small piece of glandular tissue about the size of a lentil could be found frequently attached to the capsule of the tonsil after enucleation.

Bucco-pharyngeal Ulceration of Undetermined Ætiology [*Abridged*]

By Kenneth Harrison, F.R.C.S.

The contribution embodied observation of painful recurrent ulcerations of the buccal, pharyngeal and laryngeal mucosa in 7 adult patients.

These ulcers appear to run a typical clinical course, being consistently recurrent, extremely painful, and very resistant to treatment. The buccal site is the commonest. Starting as a small red papule-of pin-head size, the initial discomfort is described as a smarting sensation. At this stage the patient can either see the lesion, or feel it with the tongue.

A day or so after this, the frankly ulcerative stage appears and the ulcer may spread. This active ulcerative stage lasts for two or more weeks. An area of marked congestion always surrounds the ulcer.

Pain in this active stage is severe, and is burning or throbbing in character. Movements of the ulcerated parts may produce such intense pain that the patients avoid talking and refuse to eat. Healing may then follow. This is usually complete in a week, making a cycle of four weeks for the complete episode.

The ulcers may be single, but more commonly multiple, and usually widespread over the bucco-pharyngeal mucosa.

The depth varies, sometimes only epithelium is destroyed, but usually the deeper tissues are invaded, and then the ulcer heals spontaneously, leaving permanent scarring. Remissions are quite spontaneous, occasionally the sufferers are troubled persistently by fresh recurring crops of ulcers. The exacerbations fluctuate in severity.

There is no accompanying rise of temperature, or any cervical adenitis. No marked sex distribution has been noted, and the length of history has been anything from three to nineteen years. No family history has been elicited.

In most of the cases there had been a definite history of deep emotional upset occurring, both prior to onset, and during the course of the affection.

A full clinical investigation was carried out, and a search was made for a causative bacteriological organism and the herpes simplex virus. Fractional gastric analyses and urine tests were performed, and in certain of the cases the ætiology was so much in doubt that biopsy examination was carried out. An underlying allergic cause was always searched for.

Clinical Features of a Typical Case:

E. G., female, aged 67.

Eighteen-year history of recurrent painful ulcerations, usually widespread in the bucco-pharyngeal region. Just prior to the commencement, she had received a severe mental shock in that both her husband and only son had died in unfortunate circumstances.

March 1951 she attended an outside hospital because of pain and dysphagia, and a laryngoscopy was reported "large fungating mass on epiglottis, larynx itself poorly visible". A biopsy was taken as malignancy was suspected. The histological report stated "subepithelial layers infiltrated with lymphocytes and plasma cells".

At this time she was referred to us; there was certainly ulceration and marked œdema of the epiglottis, right vallecula, aryepiglottic fold and ventricular band, but no involvement of the vocal cord. Similar smaller ulcers were also seen along the lateral border of the tongue, and on the buccal mucosa.

Since then she has been under our care for recurrent episodes of multiple ulcerations of the bucco-pharyngeal mucosa.

Treatment.—By the time the patients are seen, they have had very many different forms of treatment, both local and general, but with no curative effect. In spite of negative examination for a specific bacteriological organism, full courses of penicillin, chloromycetin and, in some cases, Aureomycin, have been tried during exacerbations, but with no real avail, and the pain has not been relieved, nor has the course of the disease been shortened.

In 1949, Distelheim and Sulzberger, and in 1950 Sigel, described how local application of Aureomycin paste (0·25 gramme capsule dissolved in 50 c.c. water) and mouthwashes of similar strength gave definite relief to painful recurrent buccal ulcerations, and aided their healing. Certainly in most of the cases local Aureomycin was found to be most effective. There has not been permanent cure, but the pain was relieved, and the healing time reduced. There has been recurrence of minor episodes, and the Aureomycin applications have been repeated; and in most cases have been effective.

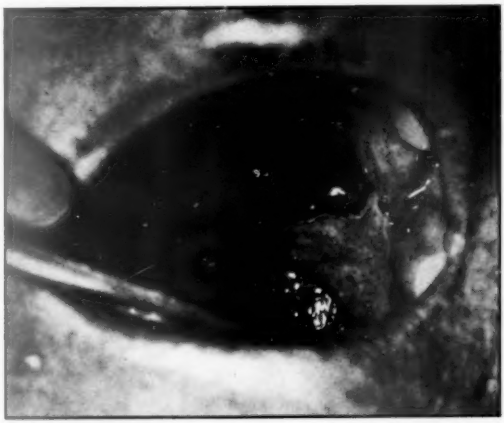


FIG. 1.—Ulcer of faucial region treated successfully by deep X-ray therapy.

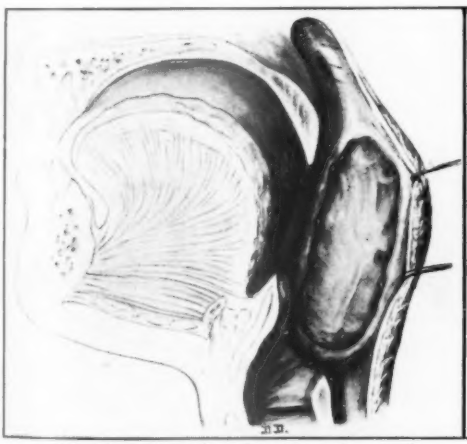


FIG. 2.—Extensive ulceration of posterior pharyngeal wall treated successfully by application of Aureomycin paste.

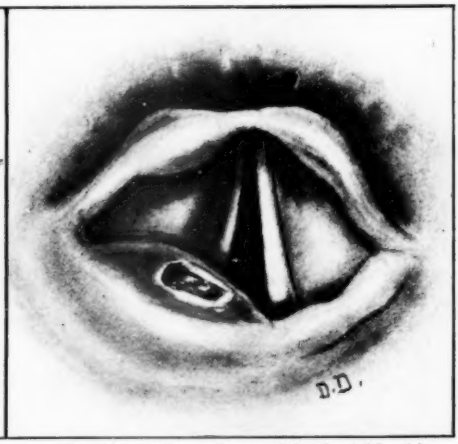


FIG. 3.—Ulcer of aryepiglottic fold, this, too, healed satisfactorily following application of Aureomycin paste.

In 2 patients, one with pharyngeal ulceration just below the level of the aryepiglottic folds, and the other with an extensive ulcer of the left faucial region (Fig. 1), deep X-ray therapy was given. A course of "anti-inflammatory X-rays" was used, and doses of about 100 r were given at weekly intervals for about ten weeks. In both cases there was permanent healing, and as yet no recurrence has taken place in those particular regions. One of the treatments was four years ago, and the other, one year. This form of treatment was used because at the time all other methods had failed to relieve the symptoms. Along with the different methods of therapy, it is important to reassure the patients, as their morale is low, because some of them believe that they have "cancer".

Conclusion.—The results are presented of a clinical investigation of recurrent bucco-pharyngeal ulceration in adult patients.

So far, no specific ætiological factor has been found, but it does appear that some severe psychical disturbance is concerned. A careful search failed to isolate the herpes simplex virus.

The relief of pain and healing of the ulcers by using local Aureomycin in the form of a paste and mouthwashes is stressed.

REFERENCES

DISTELHEIM, I. H., and SULZBERGER, M.B. (1949) *J. invest. Derm.*, **13**, 115.
SIGEL, H. (1950) *Conn. St. med. J.*, **14**, 500.

Mr. H. McIntyre had had a case similar to those described by Mr. Harrison, that of a male wholesale fruiterer, aged 24. He complained of severe and painful ulcers developing in crops of three or four which coalesced sometimes to three-quarter inch in diameter. All investigations were negative, and the condition was alleviated, though not cured, by intensive vitamin therapy and oral hygiene. Six months later his condition had relapsed and the treatment was repeated. One month later, the condition had cleared, apart from some scarring. The patient was mentally much happier, having terminated an unhappy engagement.

Mr. Scott Stevenson said he felt sure that these ulcers were not all of the same origin, but many were due to avitaminosis. Sometimes, he thought, they were affected by artificial dentures, though an element of susceptibility must be present. He personally had treated such cases, though perhaps less extensive, by giving them 200 mg. ascorbic acid three times a day, and when this was done every day many of them cleared up.

Mr. R. D. Owen said these cases had been worrying him a great deal. Pappworth (1941) described this condition as "Cyclical mucosal ulceration", because of the association between the mouth and vaginal ulceration. He based the ætiology of the syndrome on hormonic deficiencies. With regard to the symptoms, the intense pain that those people suffered from—was most striking—particularly when the ulcers were on the base of the tongue and in the pyriform fossa.

In Mr. Owen's opinion the best method to relieve those people of the pain was to apply light diathermy coagulation to the ulcerated area. 2 of his cases later developed complications. One had iridocyclitis leading to blindness, and another had pernicious anæmia.

REFERENCE

PAPPWORTH, M. H. (1941) *Brit. med. J.*, i, 271.

Mr. C. Hamblen-Thomas said that recently he had 2 interesting cases of deep ulceration with scarring at the angle of the mouth which healed regularly with potassium iodide but recurred. They were negative to all tests for syphilis.

He thought that this type of recurring deeper ulcer was of a different character from the painful superficial recurring ulcer of the buccal mucous membrane. No organisms can be grown from either ulcer. Painting the latter ulcer with silver nitrate solution eased the pain at once, but did not prevent others from occurring.

Miss Josephine Collier referred to a woman patient who had recurrent ulcers of the kind Mr. Harrison described which appeared in the course of a malignant granuloma of the nose. The ulcers in the mouth cleared up but appeared again with exacerbations of the granuloma. This ultimately proved fatal. Specimens had been shown to the Pathological Society and would be reported in greater detail later.

Mr. William McKenzie had had a patient who had precisely the same type of ulceration as Mr. Harrison had presented. He was transferred for treatment with vitamin B. Within a year he was dead with tuberculosis. There was no sign of any active disease in the chest when he was first investigated.

The Significance of Alveolar Osteitis in Rhinology

By H. G. BEDFORD RUSSELL, F.R.C.S., and LESLIE WRIGHT, L.R.C.P., M.R.C.S., L.D.S.

Mr. H. G. Bedford Russell: Low-grade osteitis of the cancellous bone of the maxilla is a common cause of infection of the submucous layer of the mucosa on the antral floor; and both are common conditions which lead to much sub-health in adults. Biopsies in such swellings reveal the presence of dental streptococci in the submucosa. Such osteitis may derive from infection through or around any maxillary tooth: streptococci evoke œdema rather than pus, and suppuration is rare. Diagnosis is radiological.

Fig. 1 shows pronounced œdema of the mucosa on the left antral floor, seen in contrast with the shadow of lipiodol. The homolateral central incisor had been devitalized, and was infected by a hæmolytic streptococcus. Fig. 2 shows disappearance of the swelling after removal of the incisor. Fig. 3 shows œdema of the mucosa over the first molar tooth, the health of which is suspect. Fig. 4 shows normal mucosa posteriorly with considerable swelling of that overlying the first molar, the bone about which shows infective absorption.

FIG. 1.—

FIG. 3.—

FIG. 1.—Shows the lipiodol shadow raised above that of the antral floor on left side, by œdema of the mucosa associated with infected central incisor.

FIG. 2.—Shows return of left antral mucosa to normal after extraction.

FIG. 3.—Œdema over one tooth, the health of which is suspect.

FIG. 4.—Shows normal mucosa posteriorly; with œdema over first molar, about which there are pockets in infected bone.

The osteitis often persists even after edentulation, as may the antritis. Treatment is removal or at least decortication of all the cancellous bone, with antral exenteration in severe cases—a procedure which is well tolerated and is successful.

Mr. Leslie Wright: Alveolar osteitis may be both inflammatory and infective. The disease spreads to adjacent structures such as the antral floor and mucosa.

Predetermination of size of the teeth was stated, and eight slides were shown illustrating:

A. Reduction in size and power of the dental bones.

B. The presence of rarefaction during alveolar process development. Fig. 1, aged 11.

C. Impaction and malocclusion.

Alveolar inflammation early sets up a serous discharge into gingival spaces which are readily infected.

To illustrate systemic effects several cases were described with slides. Among these strictly in line with Mr. Russell's subject, and descriptive of both adjacent disease and systemic effects, were:

A girl aged 15—piano player of great promise for over six years. Tremendously overweight to extent of greatly interfering with her playing. Fig. 2—overcrowding due to third molar impaction, and roots of first molar transgressing floor of antrum. All four first molars were removed. Upper ones

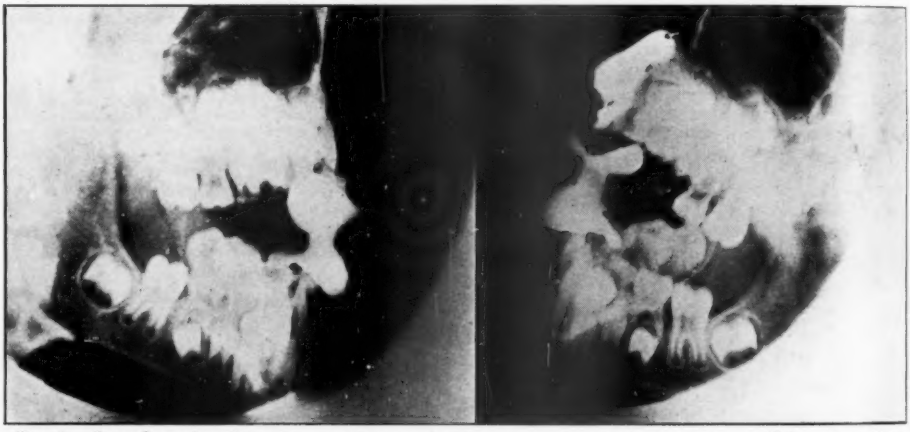


FIG. 1.—One of a series of developmental states showing encroachment of true bone mandible and maxilla.

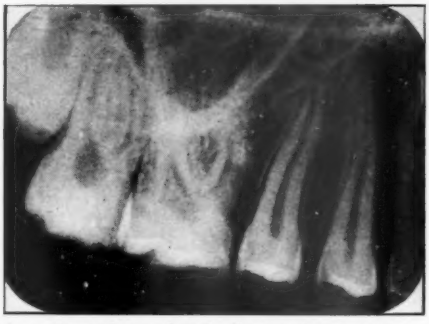


FIG. 2.—Overcrowding in molar region and early disease of first molar transgressing antral floor.

produced large antral perforations with flow of glairy mucus from both antra. Her sinusitis recovered completely in about two months, and she returned to completely normal proportions in eight months.

Figs. 3 and 4—two cases of almost identical history; both men in their forties. The tooth roots form part of the antral floor. On their removal the swollen antral mucosa of the floor was in part touching periodontal membranes.

History of Fig. 3: Several years of attacks of postnasal serous discharge and pain over antra; tendency to fainting and collapse; profuse sweating; some cardiac embarrassment throughout adult life; severe reactions to adrenaline injections; suffered from undue fatigue.

Both these cases had all teeth extracted in upper jaw. This was followed by alveolectomy including antral floors, and polypoid mucosa attached thereto. Both were cured of all their symptoms, and there was no recurrence after two and twelve years respectively.

I remember that in 1912 the subject of alveolar disease was under extensive bacteriological research in Dr. John Eyre's laboratories at Guy's. He it was who performed a lower jaw alveolectomy for biopsy in 1908.

I followed this work closely, and for years did many cases with him. It will be understood that having had experience of some 3,700 cases since 1913, I do not consider that antibiotics are essential, though to-day they are invaluable. A complete alveolectomy with edentulation—or for the edentulous—with sinus surgery, is in no way a severe surgical procedure.

The aims of the operation are:

A. The complete eradication of all alveolar cancellous bone.
B. The removal of diseased bone of the antral floor, in part or wholly.
C. The presentation in the wound of firm smooth bone edges, including any antral opening.
D. The introduction into the cleared diseased area of a soft tissue blood supply.

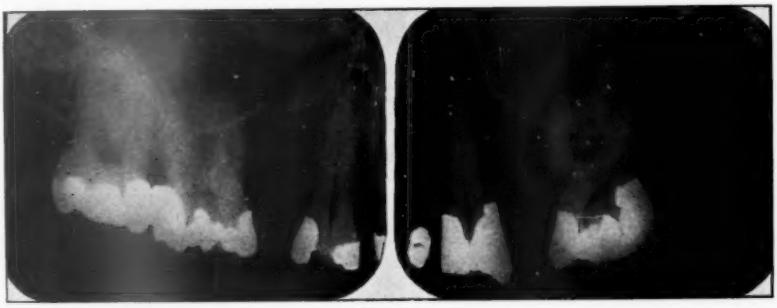


FIG. 3.

FIG. 4.

FIGS. 3 and 4.—Adult examples of the condition shown in Fig. 1. Various stages of diseased roots forming antral transgressions.

A further case was that of Mrs. G. She had been in my care for over twenty years, with history of pneumothorax prior to that. There were no physical signs of pulmonary tuberculosis over all that time. Recurrent febrile attacks, especially in the winter.

Patient herself dreaded the loss of her teeth, yet the time came when serious general ill-health would have resulted by keeping them. Patient's physician and specialist both begged me not to remove more than one or two at a time; yet through my knowledge of the patient over years, this would have been psychologically a disaster.

I removed fourteen teeth in all, plus alveolectomy. There was œdematous antral mucosa localized over one molar.

Five weeks later the patient's denture restoration was complete, and her health was satisfactory. Since then there have been no further febrile attacks.

Important features in the operative procedure were then described. It was made clear how the antral mucosa could respond to, or become infected by, every upper tooth.

Points of diagnosis were given, stress being laid upon hyperæmia at and above the gum reflection line, and the danger of the presence of Vincent's organism in the gingival discharge.

Vaccine therapy was used considerably years ago. Unless surgical measures came first, in severe cases marked reaction followed, often with skin manifestations. After operation, these phenomena were much more rare. This might well be said of antibiotics to-day which occasionally produce an allergic state.

Mr. Gordon Ashcroft: Mr. Bedford Russell and Mr. Leslie Wright have stressed the fact that it is not always sufficient to extract infected teeth, that areas of infected alveolar bone or soft tissue may remain contained within the alveolar ridges following the extraction. We can be satisfied that complications from alveolar osteitis, be they systemic or ear, nose and throat, do occur. There is a weight of evidence in support. We must, however, keep a true perspective in this matter if we are to avoid a return to a period of mass extractions of teeth with minor deviations from the normal.

The possibility that the teeth may be the host and not the source of disease should be recognized, especially in rhinological disease. The prevention of retained areas of alveolar osteitis requires a general improvement in the surgical approach of the dentist and an improvement in his operating facilities.

A complete radiographic picture should be obtained. Pre-operative prophylactic measures, scaling of the teeth, interdental dressings, and stimulating massage, must be performed when possible. The extractions should be carried out under a selected antibiotic cover. Where an acute infection exists, the extractions are postponed until it has subsided. All areas of infection are removed with a curette or dental drill. Healing may be assisted by the use of one or more penicillin tablets, 15,000 i.u., placed within the cavity so formed. Where pyorrhœa exists a gingivectomy is executed at the time of the extractions together with the removal of the affected alveolar crest.

The establishment of a healthy clot is essential; without it, the supporting framework of new socket bone does not form. The outer compact plate of bone is left unsupported and unprotected, to encounter infection and traumatic stresses, which result in progressive absorption. This can result from infection of the clot, excessive mouth washing, and the use of a high adrenaline content in a local anæsthetic.

Following the gingivectomy, the interdental septa are removed, then small V-shaped cuts are made in the outer compact plate, in the central, canine and third molar areas.

The outer compact plates are collapsed towards the lingual, the wedge cuts allowing for the narrowing of the arch. This provides a small blood clot, and two raw cut surfaces of mucous membrane, which can be sutured. Rapid sealing and healing of the sockets result, assisted by the undisturbed blood supply and the mucous membrane of the outer plate. Immediate dentures provide an additional protection, and an additional stimulus to bone regeneration, namely mastication. Post-operative attention is directed to oral hygiene. It is only by such a technique that we can provide an adequate surgical toilet and satisfactory protection to healing tissues, with a rapid return to normal habit of the patient.

Section of Urology

President—ARTHUR JACOBS, F.R.F.P.S.

[*May* 22, 1952]

DISCUSSION ON THE CHRONICALLY DILATED URETER [*Abridged*]

Mr. D. S. Poole-Wilson: In attempting to classify cases of mega-ureter the chief difficulty is the decision as to whether the dilatation is due to a lesion directly affecting the ureter itself (primary mega-ureter) or to back pressure arising from an obstructive lesion in the lower urinary tract (secondary mega-ureter). In the adult the distinction can usually be made; in children, especially in bilateral cases, the problem may be extremely difficult and ultimately only decided by the passage of time. Table I shows the main categories of chronic ureteric dilatation in each group:

TABLE I.—THE CHRONICALLY DILATED URETER

Primary mega-ureter—Dilatation arising from a lesion directly affecting the ureter.

1. Infection
   - Pyogenic
   - Tuberculous
   - Bilharzial
2. Obstruction within the ureter
   - Calculus
   - Tumour
   - Valve
   - Stricture
3. Obstruction of ureter from without
   - Aberrant vessel
   - Post-caval ureter
   - Peri-ureteric fibrosis
4. Ureterocele or stricture of ureteric orifice
5. Ectopic ureter
6. Associated with duplication
7. Idiopathic mega-ureter

Secondary mega-ureter—Dilatation arising from so-called "back-pressure effects" due to:

1. Obstruction in the urethra or at the bladder neck
2. Chronic contraction of the bladder
   - (*a*) Chronic infection
   - (*b*) Tuberculosis
   - (*c*) Interstitial cystitis
3. The neurogenic bladder

SECONDARY MEGA-URETER

There are long lists of the many lesions in the urethra and at the bladder neck which may give rise to chronic vesical retention and the gradual onset of dilatation of the ureters. In the adult the ravages of neglected prostatic hypertrophy or stricture formation are well known. In early adult life the gradual and often unrecognized progression of chronic retention resulting from Marion's disease, posterior urethral valves or unrecognized nervous disease, is a very real danger. In infancy and childhood the insidiousness of onset and the difficulties of diagnosis reach their peak. Instrumentation may be difficult and fields of view with endoscopic instruments very small. At times it may be almost impossible to decide whether a bladder-neck obstruction is due to Marion's disease, posterior urethral valves or neurogenic causes.

The following illustrative cases were then shown:

(1) Anterior flap-valve at the bladder neck causing chronic retention with gross bilateral hydronephrosis.

(2) Marion's disease or fibrosis of the bladder neck.

P. H., boy, aged 6½ years. Chronic retention with a functionless left kidney, and gross dilatation of the right kidney and ureter. Wedge resection of the bladder neck carried out on October 16, 1950. The bladder now empties and the child's condition has improved. The left kidney remains silent and the right hydronephrosis and hydro-ureter have not decreased in size.

(3) Chronic retention, bilateral hydronephrosis and mega-ureter occurring in a young girl from minor obstruction of unknown origin at the bladder neck.

R. A., girl, aged 5½ years (April 1937). Difficulty in micturition. Mild pyuria. Investigation revealed slight chronic retention. The bladder was trabeculated. No obstructive lesion was found at the bladder neck. The right kidney and ureter were grossly dilated and appeared functionless. The left kidney and ureter showed mild hydronephrosis and hydro-ureter. During micturition the bladder partially emptied itself into the right ureter. The girl was treated by dilatation of the bladder neck, as a result of which micturition became apparently normal and her urine clear. She now (1952) complains of no urinary trouble. An I.V.P. shows no function of the right kidney. The left kidney appears normal. The bladder outline is not clearly defined and the bladder does not empty quite completely with micturition.

(4) Valve of the anterior urethra causing chronic retention and gross bilateral hydronephrosis.

J. D. G., boy, aged 3¾ years. Chronic retention due to urethral valve just distal to peno-scrotal junction. During micturition visible distension of the urethra occurred proximal to the valve. Excision of valve (18.5.52). Micturition now free and incontinence has ceased.

(5) Bilateral hydronephrosis and mega-ureter due to urethral calculi.

J. L., boy, aged 7¼ years. Developed acute retention due to urethral calculi (2.2.48). A meatotomy was performed and the calculi removed. Subsequent examination revealed gross bilateral hydronephrosis and hydro-ureter. Following removal of the calculi the child passed urine well and had no chronic retention. The boy has since been kept under continuous review. A calculus formed in the left kidney and was removed in 1951. Reassessment this year shows the presence of apparently stabilized bilateral hydronephrosis and hydro-ureter with no residual urine in the bladder. It is possible that this boy is really a case of bilateral idiopathic hydronephrosis and hydro-ureter with stone formation. He has been classified as secondary mega-ureter since calculi in the urethra had caused acute retention at the onset of his trouble.

Primary Mega-ureter

No attempt was made to review all the causes of primary mega-ureter as it appeared more desirable to consider idiopathic mega-ureter in greater detail. The following illustrative cases were, however, shown:

(1) Mega-ureter resulting from chronic infection.

J. R., girl, aged 12 years (26.6.46). Right hydronephrosis and mega-ureter apparently resulting from chronic infection. Urine sterilized under full courses of urinary antiseptics. Condition of right hydronephrosis and hydro-ureter has now remained unchanged over a period of six years.

(2) Post-caval ureter causing mega-ureter.

Miss T, aged 45. Moderate hydronephrosis and gross dilatation of upper two-thirds of ureter.

(3) Ureterocele causing mega-ureter.

B. G., aged 1 year (February 1950). Ureterocele involving lower ureteric orifice of a complete duplication of the right ureter and pelvis. Gross dilatation of upper pelvis and ureter; moderate dilatation of lower pelvis and ureter. Marked recovery of hydronephrosis and hydro-ureter following excision of ureterocele (6.2.50).

(4) Mega-ureter in an ectopic ureter.

L. B., girl, aged 3 years 11 months (October 1950). Hydronephrosis and mega-ureter arising in an ectopic ureter. Complete duplication of the right pelvis and ureter. Ectopic ureter from upper segment opening just below external urethral orifice. Right nephrectomy (16.10.50).

(5) Bilateral incomplete duplication of pelvis and ureter giving rise to gross hydronephrosis of the upper pelvis and accompanying mega-ureter on either side.

E. H., girl, aged 5½ years (September 1949). The duplicated ureters united either in the intramural region or immediately without the bladder wall. The upper renal segment and two-thirds of the accompanying mega-ureter were removed on either side (24.10.49 and 21.11.49).

Idiopathic Mega-ureter

In this group are gathered those cases of mega-ureter in whom no obvious cause exists to explain the dilatation. The diagnosis is made by a process of exclusion and is, of course, most firm when the condition is unilateral. Bilateral cases do occur but before accepting them it is well to be certain that the condition has been present for a considerable time, that there is no evidence of obstruction in the lower urinary tract and that no residual urine is present in the bladder.

A typical example of mega-ureter will present the following features:

(1) The condition is usually unilateral.

(2) The urine is uninfected. Infection and the development of pyonephrosis may occur.

(3) An I.V.P. may reveal a dilated ureter, the dilatation being commonly more marked at the lower end. The ureter may, of course, be grossly distended in its full length and associated with varying degrees of hydronephrosis. When renal damage is advanced the kidney may be functionless. A post-micturition bladder film should show no residual urine.

(4) Cystoscopy should reveal no abnormality of the ureteric orifice on the affected side. A catheter should run easily into the ureter, but at times may be held up by mucosal folds in the lower end of the ureter. I have never been able to satisfy myself in these cases regarding the diagnosis of strictures of the lower end of the ureter by the passage of ureteric catheters. A retrograde pyelogram and ureterogram should reveal the dilatation of the ureter and any accompanying pelvic and calyceal dilatation. Films taken following withdrawal of the ureteric catheter reveal slow emptying of the ureter.

Ætiology

No really satisfactory explanation of this condition has yet been advanced. Excised ureters have shown no definite anatomical defects. The condition does, however, appear prone to occur in conjunction with other congenital defects of the urinary tract. Two of my own cases had single kidneys.

The possibility of a disturbance of the autonomic system affecting the whole ureter has to be considered but seems very improbable.

The most commonly accepted view is that a neuromuscular dysfunction or state of achalasia exists at the utero-vesical junction.

The presence of this neuromuscular dysfunction is not readily explained. The condition may at first appear analogous to Hirschsprung's disease, but there are many objections to this point of view. Amongst my own cases of idiopathic mega-ureter there are no instances of Hirschsprung's disease. Twistington Higgins has also stated that amongst his patients suffering from Hirschsprung's disease he has failed to find any unusually high incidence of mega-ureter.

There is also no real analogy between bowel and ureteric movement. It seems to be now generally accepted that, although there are sympathetic and parasympathetic fibres in the ureter, there are no ganglion cells. There is no equivalent to Meissner's plexus or Auerbach's plexus in the colon and no obvious mechanism for the establishment of local reflex movement. Contact with the nervous system also appears unnecessary for ureteric movement: it may be observed when the ureter has been completely removed from the body. In one of my own cases ureteric movement persisted for twenty minutes following a complete nephro-ureterectomy (including the ureteric orifice) for mega-ureter. The ureteric contractions were well marked but the ureter did not empty itself through the ureteric orifice. No lesion was found at the ureteric orifice. Ureteric movement may apparently also take place in the absence of urinary flow. In ectopia vesicæ ureteric movement may be observed at a ureteric orifice weeks or months after the ureter has been transplanted into the colon. There would thus appear to be a form of autonomous movement in the ureter. The autonomic system may act on the pelvis and ureter as a regulator of the peristalsis and a controller of tonus in these organs.

The dynamics of the ureter are still very poorly understood. No anatomical sphincters have been demonstrated in the ureter yet a segmental action appears to occur in the propulsion of urine. Idiopathic hydronephrosis appears to be due to spasticity at the pelvi-ureteric junction. It is possible that a similar spasm may occur at the uretero-vesical junction. In this region, however, the position is complicated by the ureter running through the bladder wall, contraction of which may also be a cause of obstruction.

Spasm of the ureter at the uretero-vesical junction may theoretically be due to either overaction of the sympathetic system causing relaxation of the ureter but spasm of the uretero-vesical region, or to absence of parasympathetic action giving rise to lack of tonus in the ureter and non-relaxation of the uretero-vesical region. The degree of action of the sympathetic and parasympathetic systems in the kidney and ureter is, however, not really known. Nareth aptly states that the views that the sympathetic system causes a decrease in mobility and tonus of the detrusor part in all sections but increase in contraction of the sphincters, and that the vagus causes increased mobility of the detrusor parts but relaxation of the sphincters—probably err in simplicity.

Sympathectomy has been recommended as a treatment for mega-ureter by section of the pre-sacral nerve (superior hypogastric plexus). The results have, however, been inconsistent. It is therefore perhaps worth while to consider the nerve supply of the ureter.

The renal pelvis and upper segment of the ureter receives its sympathetic supply from the cœliac, superior mesenteric and renal plexuses. The fibres follow the renal artery.

The parasympathetic supply is usually described as coming from the vagus via the cœliac ganglion. Professor G. A. G. Mitchell, to whom I am greatly indebted for much help, informs me that there is a probability that the parasympathetic supply of the ureter may come entirely from the sacral segments via the hypogastric plexus, the pre-sacral nerve and the pre-aortic plexus and its branches to the ureter.

The mid-portion of the ureter receives its sympathetic supply from the spermatic and superior hypogastric plexuses. The lowest section is supplied through the inferior hypogastric (pelvic) and vesical plexuses.

The connexions of the sympathetic system are such that division of the pre-sacral nerve alone in no way ensures complete sympathetic denervation of the lower end of the ureters. Such extensive resections would be necessary as to render the procedure unjustifiable.

Progress of the Disease

It seems probable that, in cases of true idiopathic mega-ureter, the progress of the disease is slow. In some instances, after a certain degree of dilatation has been reached, it is possible that the condition may stabilize itself. In the absence of infection the ureter remains supple and contractile, even though the kidney may be completely destroyed by hydronephrosis. It is, however, doubtful if such a ureter, even after treatment, is capable of shrinking to its normal calibre. Chronic infection, of course, gradually causes fibrosis of the wall of the ureter and surrounding tissues with the formation of permanent deformity. Even though such a ureter may be markedly kinked on itself I have never seen evidence of true stricture formation or organic obstruction.

Treatment

In the absence of exact knowledge of the ætiology of this condition, treatment must be empirical. A conservative outlook is desirable. When symptoms are minimal (perhaps confined to occasional mild loin pain), infection absent or controllable, and the lesion confined to mega-ureter with only a minor degree of renal dilatation, then it is well to avoid immediate operative procedures, a watching policy should be adopted and the course of the disease observed for months or years by periodic intravenous or, if necessary, retrograde pyelograms. In some instances the condition will thus be shown to have stabilized itself and no further treatment is necessary. If, however, it is progressing, then more active treatment may be advisable.

Various drugs have been recommended for increasing ureteric tone and mobility. Of these I have no practical experience.

As regards surgical procedures, sympathectomy by division of the pre-sacral nerve has been advised. Again I have no personal experience. Results in the literature are variable but on the whole disappointing. In this respect it must be remembered that division of the pre-sacral nerve does not cut off completely the sympathetic nerve supply to the lower ends of the ureters and it is therefore not surprising that the ultimate findings are inconclusive.

When the degree of mega-ureter is great and the kidney a functionless hydronephrotic or pyonephrotic organ then nephro-ureterectomy is the ideal form of treatment. It is usually desirable to remove the whole of the ureter as infection persisting in the lower segment of a dilated ureter may cause persistent pyuria and chronic cystitis.

If investigation shows that the mega-ureter is increasing and is accompanied by renal dilatation and diminishing function, then, and more especially in the presence of infection or bilateral disease, attempts must be made to facilitate the outflow of urine from the affected ureter into the bladder. To achieve this end the dilated ureter has at times been joined to the bladder by a side-to-side anastomosis without any separation of its lower end. More commonly the lower end of the ureter has been divided and the ureter reimplanted into the posterior or supero-lateral surface of the bladder. I have no experience of carrying out a side anastomosis. On theoretical grounds this operation does not appeal to me as there appears to be a danger of the lower end of the ureter remaining dilated and a site of chronic infection. In my own small series of cases I at first divided the ureter at its junction with the bladder, removed any excessive length of ureter and made a large anastomosis between the open end of the ureter and an opening made in the supero-lateral wall of the bladder. Care was taken to make sure that the anastomotic opening was at least a centimetre in diameter. Later it seemed probable that better results might be obtained by reimplanting the ureter closer to its normal site. More recently therefore the whole of the lower end of the ureter together with the ureteric orifice and a small margin of surrounding bladder has been excised. Any redundant ureter is removed and the lower end of the ureter then anastomosed to the opening into the bladder. The ureter therefore discharges at its original site into the bladder but through an entirely new orifice. The anastomosis of the ureter to the bladder is made by suturing the ureteric margin to the mucosal surface of the bladder with interrupted 5/0 plain catgut. The peri-ureteric tissues with the outermost wall of the ureter are then lightly sutured to the muscularis of the bladder by a few interrupted fine chromic catgut or silk sutures. By this means it is hoped to avoid stenosis at the anastomosis.

Results of Treatment

Eight cases have been treated. Originally the group was more numerous but in several instances a waiting policy has shown that the mega-ureter has been due to infection or to mild bladder-neck obstruction with the result that these patients have had to be removed from the category of idiopathic mega-ureter.

The 8 cases may be grouped as follows:

Idiopathic mega-ureter:
8 cases—3 bilateral
5 unilateral (2 with single kidneys)

Treatment:

(*a*)	Observation only	1
(*b*)	Nephrectomy and partial removal of ureter	1
(*c*)	Nephro-ureterectomy	2
(*d*)	Excision of lower end of ureter and reimplantation into bladder	
	(1) Implant on postero-superior wall	2
	(2) Implant at original site of ureteric orifice	2

No deaths occurred in the series. Brief histories of the cases, which were illustrated with slides, follow.

(*a*) *Treated by Observation*

V. B., girl, aged 3½ years (*October* 1950).

Mild bilateral mega-ureter. Condition more marked on the left side; the left renal pelvis was slightly dilated. Investigation revealed no cause. A mild *B. coli* infection was present for a short period but cleared entirely with urinary antiseptics. The child remains well. The mega-ureters have not changed during the past year and a half.

(*b*) *Nephrectomy and Partial Removal of Ureter*

S. H., girl, aged 6 years (*January* 1947).

Investigation revealed a large left pyonephrosis and gross mega-ureter. The right kidney appeared normal. No evidence of obstructive lesion of lower urinary tract.

Left kidney and two-thirds of ureter removed (10.2.47). Subsequent course uneventful.

(*c*) *Nephro-ureterectomy*

I. M. A., boy, aged 10½ years (*October* 1950).

Investigation revealed gross left hydronephrosis and mega-ureter.

Left nephro-ureterectomy (October 1950). The ureter was grossly dilated to within 2 cm. of the bladder. The lower segment appeared to join the lateral aspect of the grossly distended portion (at cystoscopy the ureter was easily catheterised).

Subsequent course uneventful. Urine sterile.

H. E. C., girl, aged 11 *years* (*February* 1952).

Left hydronephrosis and mega-ureter. Functionless left kidney. Right kidney and ureter normal. No evidence of bladder-neck obstruction.

Left nephro-ureterectomy with ureteric orifice (10.3.52). The ureter showed peristaltic contractions for twenty minutes following removal but no urine came from the ureteric orifice.

Sections of the terminal portion of the left ureter were examined by Professor G. A. G. Mitchell, who reported no significant variations from the normal. A few small bundles of nerve fibres were seen alongside vessels but no nerve cells were detected.

(*d*) *Excision of Lower End of Ureter and Reimplantation of Ureter into Bladder*

(i) *Implantation into postero-superior wall.*

I. M. F., male, aged 29.

Gross bilateral mega-ureter. Right renal and ureteric calculi (the ureteric calculi were lying free in the gross mega-ureter). Left renal stag-horn calculus.

Operations: (1) Removal of right ureteric calculi and reimplantation of ureter into fresh site on postero-superior surface of bladder (15.8.50). (2) Right nephro-lithotomy (16.1.51). (3) Left nephrectomy (6.2.51).

This patient had a stormy convalescence following the reimplantation of his ureter. He now remains well. I.V.P. (May 1952) shows good excretion from the right kidney but a little more dilatation than previously.

H. P. L., girl, aged 18 (*April* 1950).

Bilateral mega-ureter. Stone lying free in right mega-ureter.

Operation (25.7.50): Stone removed from right ureter. Transplantation of ureter into postero-superior surface of bladder.

This girl has since remained well. An I.V.P. during November 1950 showed good excretion from each kidney and no change in the renal pelves or calyces. The lower end of the right ureter was not seen and was thought to be emptying freely into the bladder. An I.V.P. during March 1951 did not show the right kidney. The left kidney appeared normal and the left mega-ureter remained unchanged.

(ii) *Implantation at original site of ureteric orifice.*

I. B. L., boy, aged 6½ (1946).

Gross hydronephrosis and mega-ureter in a single right kidney. Boy first seen in 1946. Investigation revealed a very large right hydronephrosis with gross mega-ureter. The left kidney and ureter were absent. A mild urinary infection was present. It was decided that no surgical treatment was advisable.

During April 1951 he was again reviewed. His health was steadily deteriorating compelling him to rest in bed all day long. On examination the boy was thin and pale. A very large right kidney was palpable. The urine contained albumin and some leucocytes. Culture gave a growth of *S. fæcalis* and *B. coli*. An I.V.P. showed no excretion from the right kidney. The blood urea was 40 mg.%.

On 23.5.51 a right nephrostomy was performed. The boy's general health immediately improved. On 6.6.51 the lower 5 cm. of the right ureter were removed together with the right ureteric orifice and a small portion of the surrounding bladder wall. The distal end of the ureter was then anastomosed to the opening in the bladder. There was no evidence of a stricture at the ureteric orifice in the removed specimen. The boy made a quick recovery. The nephrostomy tube was removed on 26.6.51. He subsequently passed urine normally.

This boy has remained well and is now back at school, where he plays cricket and swims. He has gained 14 lb. in weight. An I.V.P. shows fair excretion from the right kidney. There is no change in the size of the hydronephrosis.

H. B. C., boy, aged 6 *years*. Admitted to hospital during autumn 1950 with abdominal pain following a fall. Laparotomy revealed a large central retroperitoneal mass covered with hæmorrhagic areas. This mass proved to be a large hydronephrotic kidney. No other kidney was found. A nephrostomy was performed and the child made a good recovery.

This boy was later kindly referred to me by Mr. H. M. Goldberg. During July 1951 an I.V.P. showed no renal function. Cystoscopy revealed a left ureteric orifice, which was easily catheterized. No ureteric orifice was found on the right side. A retrograde pyelogram revealed a low centrally placed kidney. The pelvis was large. The calyceal pattern was not seen in detail but suggested a centrally placed unrotated kidney. A few calyces appeared relatively normal in size.

On 17.12.51 the left ureter was exposed by an extra-peritoneal approach. The ureter appeared moderately dilated and owing to the position of the kidney was short. Half an inch of the lower end of the ureter together with the ureteric orifice was removed. The ureter was reimplanted at this site.

The boy made a good recovery. In due course when a spigot was placed in the nephrostomy tube the boy at first appeared to pass urine satisfactorily (180–200 c.c. at a time). Later micturition became less satisfactory and all efforts to encourage closure of the nephrostomy (including operative closure) were unsuccessful. A cystogram on 28.4.52 showed that the opaque fluid passed freely up the ureter and outlined the renal pelvis. The ureter did not appear dilated. Some narrowing was observed where the ureter joined the bladder, but no obstruction was apparent. On cystoscopy (28.4.52) the left ureteric orifice appeared remarkably normal. Indigocarmine introduced into the renal pelvis through the nephrostomy appeared in the bladder following gentle pressure in the kidney. The child remains fairly well but has a permanent nephrostomy.

Conclusions

No firm conclusions can be drawn from this small series of cases. It seems probable that no real progress will be made until more light is shed on the ætiology of this condition. A cautious approach to any radical treatment is indicated as a period of observation may alter the diagnosis or indicate that the condition has stabilized. Nephro-ureterectomy gives excellent results when the mega-ureter is unilateral and the kidney is not worthy of attempts at conservation. It cannot, however, be regarded as a curative operation.

No final opinion can be expressed regarding the value of excision of the lower end of the ureter and reimplantation of the ureter into the bladder. Certainly in one case remarkable immediate benefit has been obtained. Another has been a complete failure—possibly due to the very gross accompanying hydronephrosis. In the remaining 2 cases the long-term results are still indeterminate. There is, however, a suspicion that renal function may be deteriorating in the kidneys above the transplanted ureters. This may possibly be due to back pressure caused by reflux up the ureter during each act of micturition or may be the result of mild chronic pyelonephritis, which is an ever-present danger both before and after operation.

Mr. D. Innes Williams: In studying the idiopathic dilatations of the ureter one is at once struck by the paucity of the information we possess regarding their natural history. Simple histological investigations have, so far, proved disappointing and it has seemed to me that if we are to learn more of these diseases we must first define with some care the clinical types which present themselves; we must trace the development of each type over the course of many years and the effects of operations so far devised, and when we have thus obtained a clearer idea of the disorders with which we are dealing, we may perhaps identify some definite pathology. Until that time we should do well to avoid the facile explanation which is implicit in the term "achalasia", refusing to allow our researches to be cramped by the *a priori* assumption that idiopathic dilatation of the ureter must have something in common with either Hirschsprung's disease or cardiospasm.

Enquiry into 78 clinical cases of mega-ureter.—As a tentative approach to this investigation I wish to present a brief analysis of 78 clinical cases of mega-ureter in children upon whom I have been able to obtain a personal follow-up. The great majority of these children have been at the Hospital for Sick Children, Great Ormond Street, under the care of Mr. Twistington Higgins to whom I am deeply indebted (Table I).

TABLE I.—MEGA-URETER IN CHILDREN

A Series of 78 Clinical Cases

Lumbar-ureterectasis	14	Uretero-vesical protrusions	4
Mega-ureter with cystitis	12	Uretero-vesical strictures	4
Mega-ureter with gaping orifice	4	Stricture of mid-ureter	1
Mega-ureter with duplications	10	Idiopathic mega-ureter	17
Mega-ureter with bladder disturbance	6	Mega-ureter with normal lower segment	2
Ureterocele	3	Unclassified	1
			78

Incidence of the disease as revealed by post-mortem statistics.—Some type of ureteric dilatation occurred in 103 out of 2,924 necropsies at the Hospital for Sick Children: infra-vesical obstructions (42 cases) are far more common that the idiopathic mega-ureters (10 cases); in fact there can be little doubt that the statement made by some authorities that bilateral hydro-ureter is a frequent cause of death in children is erroneous and results from the overlooking of urethral valves. Primary ureteric disorders appear to be very rarely even the initiating factor of a fatal disease; in 4 out of 6 of the unilateral cases, the mega-ureter was only an incidental finding.

In considering dilated ureters in general, it is first of the greatest importance to realize that the infant's ureter becomes dilated very much more readily than the adult's or even the child's. Thus in neonatal urethral obstructions it is not uncommon for the volume of urine in the ureters to equal or exceed the volume retained in the bladder.

When the ureter is very greatly distended it may appear to be thin-walled: in fact all our cases of mega-ureter could be shown, when collapsed, to be hypertrophied and I do not think atony alone is ever responsible for more than moderate dilatation. Not only is the muscle hypertrophied, but except with severe infections and acute obstructions it is actively contractile. However, once dilatation has reached a certain stage, the circular fibres are no longer capable of obliterating the lumen, so that as the wave of contraction spreads down the ureter it does not efficiently propel the urine towards the bladder. There is an important difference here between the acutely obstructed ureter and the chronically dilated one. In the former strong contractions of the upper ureter at first force the contents down to the dilated lower segment, but as the muscle relaxes fluid flows back up again. Finally the whole ureter is tensely distended and no contractions are seen. In the mega-ureters, on the other hand, although the entire length may be constantly full of urine, muscular activity is present but it is inefficient in propelling the contents. Moreover dilatation is invariably accompanied by elongation and therefore by kinking; the kinks become fixed by adhesions and are then partly obstructive. For these two reasons ureteric dilatation has a tendency to be self-perpetuating—a fact which may easily be demonstrated in the case of infravesical obstruction. For instance, in a case of valves in the posterior urethra there was reflux into the dilated right ureter. This ureter remained palpably dilated even while there was a catheter in the bladder: kinks at the lower end allowed dye to flow up yet did not allow drainage of urine. This kidney became infected after operation on the valves and had to be removed, so that we were able to confirm the obstructive effect of the kinks. It will therefore

be clear, I believe, that since ureteric dilatation of more than moderate degree is apt to be self-perpetuating, the original cause of the dilatation may be no longer operative when the case is examined. In this connexion it is worth mentioning the observations of Greene (1944) who was able by means of repeated instrumental dilatation of the dog's ureter to produce a permanent mega-ureter with hypertrophied, hyperactive muscle and a progressive back-pressure effect on the kidneys. This work provides an experimental example of a process which I believe may often occur in the child: a transient initiating disturbance producing an irreversible change in the ureter.

Factors Capable of Producing Ureteric Dilatation

What we all have in mind in connexion with the mega-ureter is (*d*) *a functional obstruction at the uretero-vesical junction*, and in many cases no other explanation can be offered, but it will be worth discussing to begin with the possible effects of (*a*) infection, (*b*) reflux and (*c*) congenital abnormalities.

(*a*) *Infection.*—There seems little doubt that infection is capable of producing atonic dilatation of the ureter in much the same way as peritonitis produces paralytic ileus. In children this type of dilatation affects predominantly the lumbar ureter, as does the hormonal atony of pregnancy. This type, which we may call *lumbar-ureterectasis* occurs with simple urinary infection, below infected renal calculi, and below the congenital type of hydronephrosis.

(*b*) *Vesico-ureteral reflux.*—Then there was a distinct group of cases, 11 girls and one boy, with a moderate bilateral mega-ureter—again often most marked in the lumbar region. In each case there was at some early period a *severe cystitis*, and where a cystogram was performed during this stage a vesico-ureteral reflux could be demonstrated. In 5 mild cases there was a return to normal after a period of some months. In the remainder dilatation persists but during the time in which they have been followed (three to four years in most cases) it has not been progressive. It is suggested that œdema of the bladder base renders incompetent the valvular mechanism of the uretero-vesical junction during the cystitis: the force of the reflux together with the atony of the ureteric muscle is sufficient to produce a dilatation which, if severe enough, will be self-perpetuating. After the cystitis has settled, the bladder and ureteric orifices are cystoscopically normal, the only permanent change being in the ureters, which so readily become dilated during the first year of life.

(*c*) *Congenital abnormalities.*—In another group consisting of 4 girls, there was a bilateral mega-ureter associated with *widely gaping ureteric orifices*, such as have been illustrated by Marion under the heading of "béance congénitale". Although all these cases have had infected urine at one time or another, there has never been a severe cystitis nor has there been any evidence of bladder-neck obstruction. We have, of course, seen widely gaping orifices in the obstructed bladder, in tuberculosis, and in 3 cases of double ureters. In these girls, however, we have been forced to suppose that the gape is a congenital abnormality and that the free reflux which it allows, perhaps together with congenital defects of the ureteric muscle, has been sufficient to cause the dilatation.

Congenital faults in the ureteric wall might be expected to be common in the *double ureters*, and as already mentioned gaping orifices have been seen in 3: in 2 on the ureter from the lower pelvis, in 1 on a bifid ureter. In the greater number, however, the orifices have been normal in appearance, and it seems not unlikely that in some the dilatation was infective in origin. Perhaps one would have anticipated the reverse: that the infection would be secondary to the dilatation, but in 3 cases the contralateral single ureter was also affected and the dilatation was predominantly in the lumbar region. Moreover during the period under review, we have treated a considerably greater number of cases of recurrent infection in double ureters which showed no dilatation at all. In a recent case, the ureter from the lower pelvis of a double kidney was dilated down to a point approximately one inch from the bladder wall. Here it was kinked over a band and, although the hypertrophy extended only up to this point, it was very difficult to be certain whether this kink was the primary obstruction or whether the ureter already in the process of dilatation had become involved with the band.

Cases of ectopic ureter in girls have not been included in this series although in 6 out of the 7 cases which have been observed during the past three years the ureter has been dilated and it is by no means certain that a stricture at the lower end was always responsible. In one child, for instance, the ureter suddenly narrowed down at the level of the brim of the pelvis, and in another there was a saccular dilatation at the lower end. For want of a better explanation I am forced to suppose that the ectopic ureter is likely to have congenital faults in its wall as well as a strictured outlet. The localized saccular dilatation is also occasionally observed in association with congenital urethral obstruction and in the trifid ureter.

(*d*) Coming back to *urinary obstruction as a cause of ureteric dilatation*:

We may first take note of a curious group of boys in whom there appeared to have been some *temporary disturbance of bladder function*. I am not, of course, concerned with those straightforward cases of bladder-neck and urethral obstruction in which radiological evidence of ureteric dilatation precedes the clinical observation of bladder distension: these are easy enough to spot on cystoscopy and have not been included in the series. However, there were two children who had had single attacks of acute retention lasting only a few days, and who afterwards appeared to regain normal micturition. On subsequent investigation the only discoverable abnormality was ureteric dilatation,

unilateral in one case, bilateral in the other, with gaping of the ureteric orifices. In the two and three years following first investigation they have remained symptom free, the ureters are unchanged in one and somewhat improved in the other. The obvious problem here is to decide whether the transient retention could have been responsible for permanent dilatation with or without some other congenital fault. In 4 other cases, all boys, moderate bilateral mega-ureter was accompanied by serious renal failure, to which 2 have subsequently succumbed, and an ill-defined bladder disturbance. One child had a long history of urinary infection. There was never more than 2 oz. of residual urine but the bladder was flaccid, of large capacity, and poor sensation. Cystoscopy and cysto-urethrography revealed no abnormality other than reflux. The ureteric dilatation was not progressive although there was a steady deterioration of renal function. In another boy there was a history of a period of dribbling micturition, and a palpably distended bladder had been observed at another hospital. Once again, on our investigation, there was no residual urine; the bladder appeared cystoscopically normal except for slight dilatation of the ureteric orifices. These findings were confirmed at an open operation on the bladder.

Congenital obstruction at the lower end of the ureter may be of an organic nature as in ureterocele and uretero-vesical stricture. *Ureterocele* has been surprisingly uncommon in this series, considering how comparatively frequently it is seen in adult life. The degree of obstruction is seldom severe, so that the onset of symptoms may be postponed. *Uretero-vesical protrusions* of the lower end of the ureter from the upper pelvis of the double kidney have been more common. They make interesting diagnostic problems but do not require special discussion here. *Congenital uretero-vesical strictures*, on the other hand, constitute a fairly high-grade obstruction and cause a progressive deterioration of renal function. The diagnosis of stricture is not always easy to establish since catheters will not invariably negotiate an orifice of normal calibre, but if the whip-ended bougie can be introduced and is gripped, whereas larger instruments prove impossible, the diagnosis may be regarded as certain. The stricture extends throughout the length of the intramural ureter in these congenital cases and cystoscopically the orifice may appear to be raised on a slight pyramidal elevation. An extensive meatotomy may replace an obstruction to the ureter by a severe degree of vesico-ureteral reflux, and unless the obstruction was of a high grade the exchange may prove a bad one. We have had the depressing experience of observing an initial improvement, followed a year or eighteen months later by a marked deterioration. A short-term follow-up in these cases is useless.

Idiopathic mega-ureters.—In these cases the dilatation and hypertrophy extended down as far as the bladder wall yet the ureteric orifice was normal in calibre and cystoscopically of normal appearance. The solitary ureter where the contralateral organ is congenitally absent appears to be especially liable to this form of dilatation. It is difficult to decide whether this group is, in fact, a homogeneous one, or whether further subdivision will be necessary. Take first the unilateral cases. We know that the deformity may be present at birth and that provided the urine remains sterile the progress of dilatation is extremely slow, if perceptible at all. This type of case is the most familiar one in adult urology simply because of its slow progress. Exacerbation of symptoms may well be precipitated by conservative surgery as in a child of 11 who had had only a slight hæmaturia; his urine was sterile. A transvesical ureteric meatotomy was performed and thereafter the urine became infected and the condition of the kidney deteriorated so rapidly that nephro-ureterectomy was necessary.

In the bilateral cases symptoms are obviously likely to appear at an earlier stage. Two of the girls had had a severe urinary infection, but in view of the degree of dilatation I was reluctant to believe that infection alone could be the cause. One boy, who apparently belongs to this group, had had an attack of anuria at the age of 6 months necessitating temporary nephrostomy. Bilateral ureteric meatotomy was performed when he was nearly 2, and when seen last year at the age of 10 he was clinically very well although the urine was hazy and pyelograms still showed well-marked dilatation.

The 2 cases of solitary ureter have both had recurrent urinary infections. Neither has had any surgical treatment as yet.

Only those cases with stone have been included in which I could feel sure that the ureteric dilatation was the primary condition. In all the stone was rounded and freely mobile, and in 2 the dilatation was bilateral although stones were present only on one side. It is clear from 2 of these cases and from the records of several earlier ones, which I have not been able to follow up myself, that simple removal of the calculus is invariably followed by the recurrence of an extremely similar concretion. Where the ureteric orifice has been stretched or cut so that it allows reflux, the resulting tidal disturbance in the ureter prevents the recurrence of stone although it may also prevent any improvement in the dilatation.

Mention must also be made of the type of *mega-ureter in which there is a segment of normal calibre at the lower end.* One has the impression from the literature that this is the type of anatomy which most surgeons expect to find but in my experience it has been rare—only two cases in this series in addition to the child with the double ureter already mentioned. In some of these cases there is undoubtedly an extrinsic obstruction due to a band or vessel running parallel to the superior vesical artery but rather above it, and, particularly where nephro-ureterectomy is performed through one incision, such an extrinsic obstruction may well be overlooked. However, there was certainly one post-mortem case in which there was no obvious cause for the change from dilatation to normal.

Pathology

Since the demonstration of the absence of autonomic ganglia in the undilated segment of large intestine in Hirschsprung's disease, many urologists have felt that a similar pathology will be found to explain the mega-ureters, especially in view of occasional reports of co-existence of the two conditions in the same patient. However, unlike the bowel the ureteric propulsive contractions do not apparently require the intervention of a nervous reflex for their continuance; no ganglion cells are found within the muscle layers of the supra-vesical portions of the ureter and peristalsis continues in the presence of full doses of ganglion blocking drugs such as C.6. Ganglion cells are to be found in the neighbourhood of the intramural ureter but it is uncertain whether they are concerned with ureteric function and there is, as yet, no evidence that they are absent in cases of idiopathic mega-ureter. Svensen and his co-workers (1952) have suggested that certain disorders of bladder function attended by residual urine and ureteric dilatation may be due to a diminution in the number of these ganglion cells—not a complete absence as in Hirschsprung's disease—but there is at present no correlation between clinical and pathological findings and no evidence at all that the ureter alone can be affected by this lesion.

The problems posed by the co-existence of bowel and urinary disturbance are not easily disentangled. In the older literature no distinction is made between true Hirschsprung's disease and what is now known as colonic inertia; we have at Great Ormond Street observed vesical retention without evident obstruction in association with colonic inertia but not in Hirschsprung's disease. A mild hydronephrosis was observed pre-operatively in one Hirschsprung case but this returned to normal after rectosigmoidectomy and there can be no doubt that the vast fæcal masses which accumulate in either type of megacolon can be responsible for ureteric obstruction.

My views on the problems of treatment are, as yet, uncrystallized. I must again insist that a better knowledge of the natural history of the mega-ureter is essential to the evaluation of any method of treatment, and that the extremely slow progress observed in many cases may be held to contra-indicate all surgical interference. Any type of operation designed to enlarge or replace the ureterovesical junction is apt to substitute reflux for obstruction, and scarring around the operation site may eventually substitute severe organic for mild functional obstruction. I am inclined to advise nephro-ureterectomy in all unilateral cases which merit any surgical operation, and conservative surgery in bilateral cases only where there is an organic stricture, a rapidly progressive dilatation or an ineradicable infection.

References

GREENE, L. F. (1944) *J. Urol.*, **52**, 565.
SVENSEN, O., MACMAHON, E., JACQUES, W. E., and CAMPBELL, J. S. (1952) *New Engl. J. Med.*, **246**, 41.

Mr. H. P. Winsbury-White said that there was no more depressing subject in surgery than the dilated ureter in children. These children were sent to hospital in fairly large numbers. The worst cases were dead before infancy was out, and many more were dead before adolescence was complete. A few reached adult life. The patchwork which the surgeon could do helped a little and occasionally there were obvious signs of improvement. But how lucky was the patient when the dilatation involved only one side of the urinary tract and the surgeon was able to excise the ureter and kidney when the opposite side was normal. To concentrate on the ureter when the bladder remained distended was not helping to get the best results. Reference had been made by both opening speakers to the fact that calculus was a complication of dilatation. In his experience in these days the only cases of calculus which he saw in children were secondary to dilatation, apart from those few tuberculous cases which one saw in sanatoria.

Mr. A. W. Badenoch referred to the so-called idiopathic dilated ureter as seen in the child, in the young adult, or in the older adult. He had seen 16 of these cases where there was no apparent cause for obstruction. The striking thing in these cases was that, considering the gross dilatation of the ureter, the symptoms were comparatively slight.

One man, aged 46, had one attack of colic and there were eighteen stones in the lower end of the massively dilated ureter. The majority of his cases had undergone nephrectomy, but he had in mind 4 cases which had been treated conservatively. In 2 of these the ureter had been divided and the cut end of the ureter implanted in the bladder. Both these cases had to have a nephrectomy on account of acute ascending pyelonephritis within two weeks. Incidentally, he wondered why Mr. Poole-Wilson removed the lower end of the ureter. The other 2 of the 4 cases had lateral anastomosis with the ureter left in continuity. One of these was a young boy who had been quite well now for a period of a few months. The other was a woman who had remained well, but radiologically her ureter was still of the same calibre. He agreed that they ought to treat these cases medically unless there was some pathological condition other than the dilated ureter or unless the symptoms were severe enough to warrant surgery.

Mr. D. Innes Williams, taking up what Mr. Winsbury-White had said about mortality, remarked that the post-mortem statistics at Gt. Ormond Street demonstrated that the children rarely died of a primary ureteric condition. Deaths occurred as a result of lower urinary obstruction.

Mr. D. S. Poole-Wilson said that he largely agreed with Mr. Winsbury-White. Death occurred frequently in the early days of life when obstruction at the bladder neck had caused gross renal damage.

Mr. Badenoch had mentioned the question of idiopathic mega-ureter in adult life. Accurate diagnosis at this age was often difficult. He had seen several cases, which had been labelled idiopathic mega-ureter but when their early histories were investigated and the radiographs studied the diagnoses appeared at fault.

With regard to the removal of the whole of the lower end of the ureter in cases of idiopathic mega-ureter, it was felt that when the exact site and mode of obstruction in this region was not known, excision of the whole of the affected area and any redundant ureter was advisable. For idiopathic hydronephrosis, where a similar type of functional obstruction occurs, one removes in the Hynes-Anderson operation the whole area of the pelvi-ureteric junction. On the same basis in idiopathic mega-ureter one removes the lower end of the ureter and its entrance into the bladder.

[*June* 26, 1952]

DISCUSSION ON THE TREATMENT OF ANURIA

Dr. E. M. Darmady: Just over four years ago I had the pleasure of addressing the Section on the treatment of anuria by the artificial kidney (Darmady 1948*a*). At that time the prognosis of cases of anuria was extremely grave. However, in the meantime considerable strides have been made in our knowledge and I think it is fair to say that the prospects for patients of this sort are considerably brighter. This, to my mind, is due to three factors, first to a better understanding of the pathology of the kidney in this condition, second increased knowledge of the natural history of the syndrome and third the methods designed to combat the "toxæmia" of this form of renal failure.

Nomenclature of the Syndrome

Before passing to the consideration of treatment proper, I feel it is advisable to recapitulate some of the findings on the pathology of the kidney with special reference to the many ætiological factors concerned.

From the literature and from personal experience (Darmady, 1948*b*) one finds that there are well over 72 conditions which have been stated to be responsible for anuria. As a result a large number of names have arisen, some laying emphasis on the ætiological factor, others laying emphasis on the pathological lesion, as for example traumatic anuria, crush anuria, crush syndrome, blackwater fever, reflex anuria, lower nephron nephrosis, hæmoglobinuric nephrosis, sulphanilamide anuria, &c. These cases have been characterized by an acute uræmia with blood ureas rising to enormous levels. It is therefore not surprising that they were thought to be the same syndrome, and subsequent work has proved this to be so. For the renal lesion has been proved by histological methods and by dissection to be tubular changes affecting all parts of the nephron, which I feel wiser to designate as acute tubular necrosis.

Experimental Studies

Before turning to the treatment it is as well to review the literature on experimental work on this subject. Because shock seemed to play such an important part, the most emphasis has been placed on work which is followed by renal vascular embarrassment. Therefore animal experiments were designed to assess the effect of interference to the blood supply to the kidney. Such experiments proved to be successful since it was found that the kidney tissue is highly susceptible to anoxia (Scarff and Keele, 1943). For example Badenoch and Darmady (1947) found that if the renal artery was clamped for 120 minutes in a unilateral nephrectomized rabbit, the mortality rate was 100%, for 90 minutes it was 60%, whilst for 60 minutes the mortality rate was only 20%. All the animals developed uræmia and although the majority of those dying showed cortical necrosis, a few showed changes identical to acute tubular necrosis whilst the remainder recovered. Similarly Van Slyke *et al.* (1944) showed that in dogs the kidneys were more resistant to anoxia and the time of clamping could be considerably increased; the critical time was about four hours. By interpolations it can be assumed that the human kidney, being larger than the animal, is also more resistant to vascular embarrassment and the critical time probably about six to eight hours.

Association with Intravascular Pigment

Experiments in animals and man show that the normal kidney is perfectly able to excrete hæmoglobin and its derivatives, for example in paroxysmal hæmoglobinuria renal failure is rarely observed.

How then can the fact that intravascular pigment, which is so often seen in these cases, be explained? This, too, can be answered by experimental work. Yuile *et al.* (1945), Badenoch and Darmady (1947), have shown that if the rabbit kidney is damaged, either by clamping the renal arteries for a critical time, say ninety minutes, or by a sublethal dose of nephrotoxic poison, followed by an injection of stroma-free hæmoglobin, there is a striking increase in the mortality rate. From this one

can conclude that the pigment is an added factor which often prevents normal recovery. This is in keeping with clinical observations in man. One knows for example that Myanesin produces hæmolysis of blood, but it is not followed by kidney failure. However, if this drug is used during an operation which is liable to cause a strain on the kidney, the resulting hæmolysis may tip the scales and the patient develop irreversible uræmia.

In turning to the pathology of the nephron in man, Oliver *et al.* (1951) and Darmady and Daphne Richardson Jones (1950) have made a special study of the nephron by dissection, and have come to the conclusion that whatever the ætiological factor, the ultimate changes are identical. Our dissections have shown that the upper nephron, i.e. the first convoluted tubules, has shown as much damage as the remainder of the nephron. These changes are twofold, first an actual break in the wall of the tubule, and second a patchy degeneration of the tubular epithelium. As these lesions have been described elsewhere, or are in the course of publication, I do not intend to deal with them fully here; but it is because of the similarity of these lesions that we feel that acute tubular necrosis is a better name.

Two further factors confirm our view:

(1) That whatever the ætiological factor the subsequent natural history of the disease is identical.

(2) That biochemical and direct measurements both in man and animal give convincing proof that the blood flow to the kidney is reduced (Cournard *et al.*, 1943; Lauson *et al.*, 1944).

Natural History of the Syndrome

Bull and his colleagues (1950) have shown that there are three distinct phases:

(1) The precipitating phase which brings about a period of renal circulatory failure, and can be caused by shock, disturbance of electrolyte/water balance or from a reflex or allergic origin, or local disease.

(2) A period of anuria or oliguria, with retention of toxic products together with extra-renal production of faulty metabolites.

(3) A period of diuresis with abnormal excretion of electrolytes, accompanied by excessive loss of water, potassium, chlorides, sodium, calcium and magnesium.

The treatment of the first phase is therefore important, since it is a preventive measure.

Preventive Measures

There are numbers of different treatments advocated for this syndrome, many of which may have a rational basis. It is for this reason that I feel it is essential to consider the ætiological factors responsible in greater detail.

Table I.—The Ætiology of Acute Anuria

Renal circulatory insufficiency					**Disturbance of electrolyte/water balance**		**Renal circulatory insufficiency or disturbance of electrolyte/water balance with intravascular pigment**
A. General	B. Local						
Shock Severe trauma Post-operative azotæmia Severe hæmorrhage Head injury Acute pancreatitis Gunshot wounds	Reflex Ureteric calculi Emotional states Vascular injury Sulphanilamide Reflex anuria Anoxia	Local Disease Myelomatosis Acute nephritis Typhus fever Weil's disease Pyelonephritis Pneumonia Nephritis	Allergic Favism Streptomycin Serum sickness Mushroom poisoning Sulphanilamide (some forms) Pitressin Incompatible blood transfusion (some forms) Staphylococcal toxin Meningococcal toxin	Chemical Nephrotoxins Oxalate Mercury Phosphorus Cresol Carbon tetrachloride Glycol Phenol Uric acid Uranium salt CO poisoning Alloxan Bite by *Latrodectus mactans* (Black widow spider)	Pyloric stenosis Alkalosis Acidosis Addison's disease Heat stroke Hypochloræmia Hæmatemesis Dehydration	Intestinal obstruction Pernicious anæmia Diabetic coma Dysentery Cholera	Incompatible blood transfusion Burns Crushing injury Blackwater fever Hepatorenal syndrome Myanesin Yellow fever Equine paralytic myohæmoglobinuria Weil's disease Icterus neonatorum
Obstetrical Ante-partum hæmorrhage Post-partum hæmorrhage Septic abortion Eclampsia Concealed accidental hæmorrhage							

In examining the precursors of anuria by far the largest group is that caused by renal circulatory insufficiency, due either to general systemic stress or to local factors. These are given in Table I. I have further subdivided the local causes into four groups, first reflex, or of neurogenic origin, second actual diseases affecting the kidney, third allergy. The fourth, chemical nephrotoxins, unlike the remainder, shows a difference in pathological lesion in that a certain part of the tubule is picked out (Oliver *et al.*, 1951).

In the group caused by disturbances of electrolyte/water balance, the onset is often not so dramatic as in the earlier groups. It is frequently reversible, but nevertheless results in the same renal lesion, as proved by dissection. I would also add that the disturbance of electrolyte/water balance is often a deciding factor in causing death if it supervenes on any of the former conditions.

In the final group I have placed those conditions which are accompanied by either renal circulatory failure or electrolyte/water balance disturbance, and in which the production of intravascular hæmolysis or pigment is the added factor in causing death.

In my previous remarks I have tried to stress the importance of preventing the precipitating phase and shortening the period of renal insufficiency and in this way preventing irreversible renal damage. Amongst the special treatments advocated to this end have been splanchnic block and, latterly, caudal analgesia. It is claimed that such measures have been used successfully in obstetrical conditions and cases of reflex anuria. For example, one knows only too well that the removal of a stone in the ureter is followed frequently by sudden and dramatic diuresis, and it would seem logical that, if such measures are used early, striking results might be obtained. On the other hand, personal experience, and that of others, has shown that treatment by these means is frequently disappointing.

Another method has also been suggested. Olsen and Necheles (1947) tested a number of substances in animals which were submitted to standard burning with production of hæmolysis of blood. They found that, of substances tested, intravenous sodium sulphate gave the most marked diuresis and excretion of pigment. Personal experience in cases of sulphanilamide anuria has confirmed this and I have found that provided sodium sulphate is given early in the disease whilst the kidney is still intact a remarkable diuresis can be produced, thereby removing the local irritation. My experiences later in the syndrome have proved disappointing, it would seem that normal methods of preventing shock, by blood transfusions, correction of electrolyte/water balance, &c., the use of lævo-epinephrine and ACTH are indicated.

Anuric phase.—In the anuric phase there should be two main aims:

(1) To maintain strict control of water intake to match the sweat and respiratory loss.

(2) To control the accumulation of waste metabolites which occur as the result of kidney failure and also of extrarenal factors.

The waste metabolites may be controlled in one or two ways. They can be allowed to accumulate and their removal carried out by a form of dialysis of which intestinal or peritoneal irrigation or the artificial kidney have been used. The French have recently suggested a modification of the same method by using an exchange transfusion and have claimed a high recovery rate. From our point of view we have found that it is easier to prevent the formation of toxic metabolites. Both in anuria and, for that matter, the diuretic stage by far the most important factor is the control of the water balance.

No really satisfactory test has yet been developed to determine the degree of hydration of the patient. It is perfectly true that the accurate recording of fluid balance charts has gone a long way to solving this problem, but, as I have indicated earlier, anuria frequently develops in those suffering from disturbance of electrolyte/water balance and in whom hydration must be assessed before treatment starts. I have in mind cases requiring prostatectomy who already have poor kidney reserves, and who are always liable to develop anuria or oliguria during their post-operative period.

The packed cell volume of the blood or the plasma specific gravity may often be used as a serial index, but suffers from three defects (*a*) that the patient may be anæmic, (*b*) that he may develop anæmia during the course of his illness, and (*c*) that it may vary with the degree of cellular hydration as a result of electrolyte disturbance.

Cellular hydration.—Hamburger (1951) has recently drawn attention to the importance of the cellular hydration. To assess cellular hydration he has stressed the importance of the so-called effective osmotic pressure (determined by the depression of the freezing point of the plasma or the electro-conductivity of plasma). The formula is found by determining the total osmotic pressure by the depression of freezing point and deducting the theoretical osmotic pressure of the blood urea. It is claimed that as urea diffuses freely and equilibrium is easily established, it can be disregarded in determining the pressures liable to cause movement of water from cell to interstitial fluid.

In order to try and demonstrate the importance of these investigations to the patient, I have prepared a diagram (Fig. 1). The proportion of water normally found in the body is extracellular volume approximately 20%, intracellular approximately 50% of the total body water, whilst the remainder is held in bones or in chemical combination, and for the purpose of this demonstration has been excluded. The normal distribution is shown on the extreme left of the diagram. The effective osmotic pressure is shown in the space reserved for extracellular volume, expressed as milliosmols. In cases of salt depletion it is found that the effective osmotic pressure is reduced. This results in a rise of water

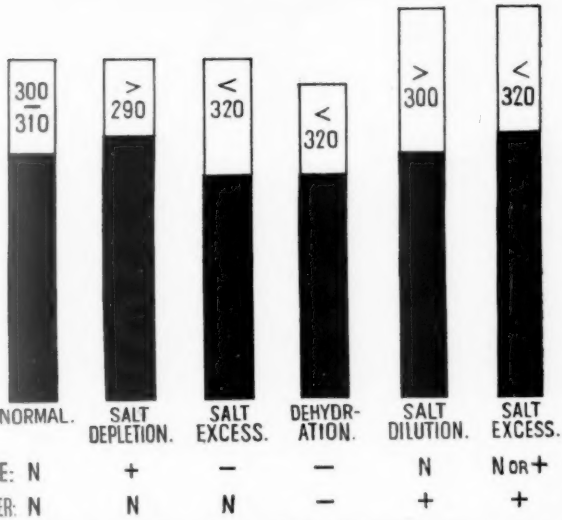


FIG. 1.—The black area represents the cellular volume, whilst the white area represents the extracellular volume. Changes in cellular volumes due to water and electrolyte are indicated by alteration in area.

volume showing hypo-hydration of the cells. On the other hand if salt excess occurs either as a result of therapy or from other reasons, the cellular water volume is reduced, whereas in dehydration the total amount of water is reduced, but as the electrolytes are concentrated within the blood there is a rise of effective osmotic pressure and reduction in cellular volume. This is relatively easy to control and is treated by giving salt in the case of the first, and water in the last two cases. During the course of any therapy the condition might also arise when the total body water is increased, and the effective osmotic pressure may be normal or below normal, more often caused by excessive intravenous therapy. If the observer mistakenly believes that the cellular volume is normal, he may give salt. In such cases he will find a condition which is invariably fatal, for if the salt concentration is too high and the cellular volume is also increased, the anuria or oliguria persists. It is therefore imperative even if it is decided not to use the high calorie diet, not to give either excess water or salt. For this reason salt should always be excluded from the diet at this stage.

Diuretic phase.—It is the third or diuretic phase which often gives the clinician the most trouble, and the assistance of the biochemical department is not only essential but vital. During this phase there is an excessive urinary loss of water which is sometimes impossible to replace by the oral route, and it may often be imperative to set up intravenous drip transfusion. The excessive loss is also often difficult to gauge. One urgently requires a machine which will weigh the patient in bed, which is after all the simplest method of judging water loss. To illustrate the difficulties of combating the water loss in diuretic stage, I would like to mention a patient whom we treated by the high calorie diet method and who was anuric for 22 days; on the 23rd day he passed 700 ml. and on the 24th day 1,500 ml., on the 25th just over 2 litres. The patient, however, was unable to absorb or take the quantity of fluid to match this output by mouth and, as the importance of keeping pace with fluid by added intravenous route was not at the time apparent, he died on the 27th day of dehydration and hypopotassæmia.

The electrolytes too are important at this stage and although sodium, calcium, chloride, CO_2 are lost heavily, the potassium is lost at an even greater rate. The danger of sudden death from cardiac arrest subsequent to hypopotassæmia is a real danger and frequent estimations are necessary. Unfortunately potassium salts are unpleasant to take and whilst it is better to give potassium in the form of fruit drinks, these often are not enough, and we have to resort to intravenous potassium infusion. For this we use 1·1% of potassium chloride or 1·9% potassium lactate according to the patient's requirements. I would strongly urge that these solutions be kept ready sterilized for use, as these cases have a habit of turning up on public holidays or on weekends when the pharmaceutical assistance is difficult to arrange.

As the state of the patient's hydration is by far the most important factor in saving life, it is important for us to develop a simple method of estimating either total body water, or the extracellular volume. At the present time the methods which have been developed are a research procedure and cannot be used as a routine measure, since they require multiple punctures and are expensive in labour and materials.

SUMMARY

(1) Prevention is better than cure, and the patient about to undergo operations causing renal embarrassment should be checked for adequate water and salt reserves.

(2) Overloading with salt and water is disastrous and contributes to the oliguria or anuria. Water control together with control of extra metabolites is essential to recovery.

(3) The control of water and electrolytes can be covered better by the estimation of the effective osmotic pressure or electro-conductivity of the plasma, but development of easy techniques for estimation of total body water and extracellular volume is essential.

I would like to express my thanks to the Medical Research Council for an expenses grant which made possible the work on which this lecture is based.

REFERENCES

BADENOCH, A. W., and DARMADY, E. M. (1947) *J. Path. Bact.*, **59**, 79.
——, —— (1948) *Brit. J. exp. Path.*, **29**, 215.
BULL, G. M., JOEKES, A. M., and LOWE, K. G. (1950) *Clin. Sci.*, **9**, 4.
COURNARD, A., RILEY, R. L., BRADLEY, S. E., BREED, E. S., NOBLE, R. T., LAUSON, H. D., GREGERSON, M. I., and RICHARDS, D. W. (1943) *Surgery*, **13**, 964.
DARMADY, E. M. (1948*a*) *Proc. R. Soc. Med.*, **41**, 418.
——, (1948*b*) *J. Bone Jt. Surg.*, **30B**, 309.
——, and JONES, D. R. (1950) *Brit. med. J.*, ii, 1,263.
——, ——, and HAWKINS, M. (To be published.)
HAMBURGER, J. (1951) Congrès Français de Médecine, 28th Session. Brussels.
LAUSON, H. D., BRADLEY, S. E., COURNARD, A., and ANDREWS, V. V. (1944) *J. clin. Invest.*, **23**, 381.
OLIVER, J., MACDOWELL, M., and TRACEY, A. (1951) *J. clin. Invest.*, **30**, 1305.
OLSEN, W. H., and NECHELES, H. (1947) *Surg. Gynec. Obstet.*, **84**, 283.
SCARFF, R. W., and KEELE, C. A. (1943) *Brit. J. exp. Path.*, **24**, 147.
VAN SLYKE, D. D., PHILLIPS, R. A., HAMILTON, P. B., ARCHIBALD, R. M., DOLE, V. P., and EMERSON, K. (1944) *Trans. Ass. Amer. Phys.*, **58**, 119.
YUILE, C. L., GOLD, M. A., and HINDS, A. G. (1945) *J. exp. Med.*, **82**, 361.

Professor G. M. Bull[1]: Anuria or severe oliguria may be due to three groups of causes:

(1) Circulatory renal insufficiency (extra-renal uræmia).
(2) Organic damage to the kidneys.
(3) Obstructions.

From 1947 onwards Drs. Joekes, Lowe and I have seen 112 patients with anuria or severe oliguria. Of these, 48 were due to circulatory renal insufficiency, 59 were due to organic renal damage and 5 were due to obstruction. The relative infrequency of obstructive anuria is due to the fact that such patients were seldom referred to us and this group will not be considered further.

(1) *Circulatory Renal Insufficiency*

This is one of the commonest and most important causes of oliguria or anuria. It is almost invariably due to oligæmia from severe dehydration or hæmorrhage but may occasionally be seen in extreme cardiac failure. The azotæmia and uræmia are as much due to renal dysfunction as in any other type, but the dysfunction is secondary to renal vasoconstriction and not to organic change.

Appropriate treatment in most cases leads to a rapid restoration of renal blood flow and renal function. If, however, the renal blood flow is very severely reduced for about one to four hours or more, or less severely reduced for a longer period, organic damage to the kidney may result. This damage is acute tubular necrosis. It is thus an urgent matter to correct oligæmia or take other appropriate steps which will improve renal circulation in any person with this type of renal insufficiency.

Not only may renal damage result from prolonged circulatory renal insufficiency but also the reverse may happen. Patients with renal insufficiency may become dehydrated from vomiting or an inability of the kidney to retain water and salt and so superimpose a circulatory insufficiency on the organic renal change. Thus in any uræmic patient we must determine whether some extrarenal factor such as dehydration or cardiac failure is present and correct it.

The principles of diagnosis and treatment of these extrarenal factors will not be dealt with.

(2) *Anuria Due to Organic Renal Disease*

Of the 59 patients in this group, 47 were suffering from acute tubular necrosis. The functional organization of the kidney in this condition and the principles of treatment have been reported in two previous papers (Bull, Joekes and Lowe, 1949, 1950) and will not be considered further. When this treatment is applied correctly at an early stage, gross disturbances of water and ion balance with consequent uræmia seldom occur. Sometimes, however, patients are seen who have been treated differently or who have complicating diseases. These present special problems in management and I will deal with some of them in more detail.

(i) *Anæmia.*—Patients who develop acute tubular necrosis following hæmolytic blood transfusion reactions or severe blood loss often remain anæmic or anæmia may be present for some other reason.

[1] This contribution is based on work done at the Postgraduate Medical School of London with Drs. A. M. Joekes and K. G. Lowe.

This state should not be allowed to persist for it constitutes one of the extrarenal factors already mentioned as a cause of reduced renal function. We routinely maintain a hæmoglobin concentration above 70% of normal by transfusion of packed cells. The volume of blood so given can be neglected in calculating the fluid requirements of the routine treatment.

(ii) *Vomiting.*—This is very occasionally so troublesome as to make it difficult or impossible to continue intragastric feeding. In this event we pass a polythene catheter into the superior vena cava (de Keyser *et al.*, 1949) and drip through it a 20–50% glucose solution so as to maintain a calory intake of 1,600 or more a day. Such a high glucose intake cannot be achieved by using a peripheral vein because of venous thrombosis, but, by infusion through a catheter, this treatment can easily be maintained for over a week and I have seen it continued for over two weeks without trouble.

(iii) *Potassium intoxication.*—In the oliguric phase of acute tubular necrosis the serum potassium concentration seldom rises to dangerous levels when the conservative treatment indicated is used. Indeed high serum potassium levels may fall as a result of this treatment.

I would stress the importance of a very high carbohydrate intake. Protein sparing may be achieved by a lesser intake of non-protein foods, but an excess of carbohydrate should be provided so that potassium is taken into the cell and stored in a harmless form with the glycogen formed from glucose.

Despite a very high carbohydrate intake dangerous rises in serum potassium may occur in grossly infected patients with a high rate of tissue breakdown, and following misguided potassium administration. When this occurs, active treatment is required.

In some departments a high serum potassium level is taken as an absolute indication for some form of dialysis. I am sure that this treatment is effective but I regard it as too complicated for routine use. There are two other methods of treatment which are simpler and safer.

(*a*) *Insulin plus glucose administration* (Bywaters and Joekes, 1948): Insulin hastens the deposition of the potassium glycogen complex already referred to. This treatment should be used in emergency and 50 units of insulin plus 50 or preferably more grammes of glucose will cause a rapid fall in serum potassium level (Fig. 1).

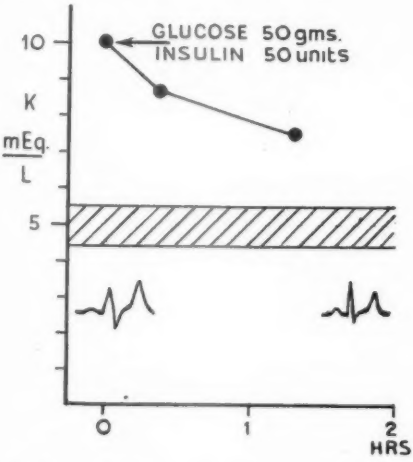


FIG. 1.—*The effect of glucose and insulin on the serum potassium level and the electrocardiogram.* Note that after intravenous injection of 50 grammes glucose and 50 units insulin serum potassium level dropped considerably and there was a change in the electrocardiographic pattern towards normal. The hatched area in the graph represents the normal range of serum potassium.

(*b*) *Ion exchange resin treatment*: In practice we have used Zeo-carb 225 in the sodium cycle in doses of 100 grammes per day for one or two days, by mouth. The Na cycle resin can be prepared as follows:

Take 200 grammes of the H cycle resin and place in a large beaker covered with crushed ice. Slowly add 1% NaOH solution, stirring vigorously until the supernatant fluid is at pH 7 on testing with a suitable indicator. Decant the supernatant fluid and wash with distilled water two or three times. Dispense.

In the same patient shown in the figure 200 grammes of Na cycle 225 removed 262 mEq. of K while a 7 litre intermittent peritoneal dialysis removed only 17·4 mEq.

(iv) *Potassium deficiency.*—This may occur particularly in the early diuretic phase of acute tubular necrosis. When urine flow recommences in this condition tubule function remains virtually absent and the urine has a composition approaching that of protein-free plasma. If a mineral free diet is continued for long into this phase the serum potassium may fall very low and paralysis result. This can best be avoided by replacing the mineral-free diet two days after 1 litre of urine has been passed by a diet containing fruit. The two days are allowed to cause the serum K level which is often slightly

elevated to drop to normal. The fruit contains enough potassium to keep an adequate potassium balance in most cases.

If the serum potassium concentration is very low it may be necessary to give potassium salts and this should preferably be done by mouth in quantities not exceeding 5 grammes per day of KCl in divided doses. At this dosage level careful watch for an overswing to hyperpotassæmia should be kept and a dose of 1 gramme per day is to be preferred where rapid and accurate biochemical control is difficult.

(v) *Infection.*—This is an important cause of death in anuria. It contributed to death or actually caused it in 8 of the 14 patients with acute tubular necrosis who died in our series. (These 14 include patients treated before the introduction of the conservative regime.)

All patients with anuria or severe oliguria should receive as a routine 1 million units of penicillin per day. A single dose of the crystalline salt is all that is required as the substance is not excreted in anuria.

Where other antibiotics are required for penicillin-resistant infections the virtual absence of renal function raises a difficult problem. Aureomycin, terramycin, streptomycin and chloramphenicol are all excreted almost exclusively by the kidney. If they are given in the usual doses they quickly build up to toxic levels in the blood. A dose of 2 grammes in the first day, of any one of them, will give an adequate blood level and not more than 1 gramme in excess of this should be given in divided doses per week thereafter.

In this account of our management of the complicated case of anuria, I have hardly touched on the most difficult aspects of control of water, NaCl and acid-base balance. As these warrant a fuller treatment I have reserved them for a future occasion. I will, however, list some techniques that we have found of value:

In diagnosis: (*a*) The use of the $CuSO_4$ method of determining plasma specific gravity for assessing states of hydration (Phillips *et al.*, 1950).

(*b*) Observation of the venous pressure.

(*c*) Estimation of serum Na or electrical conductivity of plasma.

In treatment: (*a*) Restriction of fluid intake to below the rate of insensible loss for gradual reduction of overhydration.

(*b*) Acupuncture.

(*c*) Appropriate administration of $NaHCO_3$ or NaCl as indicated.

(*d*) Two interesting techniques of which I have no personal experience, which might be employed in appropriate circumstances, are the use of anion exchange resins and the technique of electrolyte subtraction (Denton *et al.*, 1951) for correction of disturbed acid-base balance in cases where further ion administration is best avoided.

In conclusion, I would stress that the avoidance of states of imbalance is much easier than their correction.

REFERENCES

BULL, G. M., JOEKES, A. M., and LOWE, K. G. (1949) *Lancet*, ii, 229.
——, ——, —— (1950) *Clin. Sci.*, **9**, 379.
BYWATERS, E. G. L., and JOEKES, A. M. (1948) *Proc. R. Soc. Med.*, **41**, 420.
DE KEYSER, R., VAN EECKHOUTTE, P., KOP, P. S. M., and KOLFF, W. J. (1949) *Ned. Tijdschr. Geneesk.*, **93**, 2386.
DENTON, D. A., WYNN, V., MCDONALD, I. R., and SIMON, S. (1951) *Acta med. scand.* Suppl. 261.
PHILLIPS, R. A., VAN SLYKE, D. D., HAMILTON, P. B., DOLE, V. P., EMERSON, K., and ARCHIBALD, R. M. (1950) *J. biol. Chem.*, **183**, 305.

Mr. Ashton Miller: *Anuria Due to Obstruction*

I would first like to discuss briefly certain so-called "surgical" methods of treating anuria, whether due to ureteric obstruction or not.

The most dramatic of these is undoubtedly renal decapsulation, one or sometimes both sides being operated on at a time. Occasionally diuresis occurs afterwards. Some authorities believed that by decapsulation they were performing sympathectomy of the kidney because they thought that the nerve supply entered through the capsule; this is not so, of course—the only way of denervating the kidney is by stripping the renal artery and its branches of their adventitia. Others thought that the kidney was so swollen and tense inside its capsule that removal of the capsule allowed the intra-renal pressure to drop with resulting secretion of urine. For one thing the capsule has not been tense in those anuric kidneys that I have seen and if the kidney is œdematous then it is only because the whole body is œdematous from having too much fluid poured into it. Our conception of the pathology of anuria does not suggest that decapsulation can increase the chances of recovery. There is now, in my opinion, no justification at all for performing decapsulation in any variety of anuria. Spinal anæsthesia and lumbar sympathetic chain block have been used with the idea that they abolish spasm of the branches of the renal artery; by the time anuria has developed, possibly as a result of arterial spasm, the damage has already been done and cannot be undone except by a process of epithelialization. At one time, about five years ago, I thought that lumbar sympathetic block was worth trying in most cases of anuria. I had arranged to do this on a woman suffering from sulphonamide tubular nephrosis,

but I found on getting to the ward that diuresis had started. If I had performed a lumbar block earlier that day I should have been almost convinced that it had been responsible for resumption of urine secretion. Into the same category comes the intravenous injection of various solutions such as hypertonic glucose and isotonic sodium sulphate. All of them do nothing but harm by upsetting the fluid or the electrolyte balance; their use has, I think, always been based upon the fallacy that the kidneys of an anuric patient are normal and able to respond to diuretics if potent enough.

The experimental results of obstructing a ureter.—Caulk (1925) ligated one ureter in a hundred dogs and in no single case under any circumstances could he produce anuria, only very temporary cessation of function; his main object was to produce so-called reflex anuria. The vital question to the clinician is, however, how long can a kidney be obstructed and still recover? Hinman and Morison (1923) showed, in dogs, that if one ureter is occluded for less than fourteen days then the kidney will recover completely after the obstruction is removed. If, however, it is occluded for three weeks then atrophy of renal tissue occurs and all function is lost unless its fellow kidney has been removed, when some recovery will occur. It appears that after fourteen days all function is taken over by the normal kidney, which will then never give it up; removal of the normal kidney provides the stimulus necessary to prevent atrophy of the occluded one. No real explanation of this mechanism has ever been given.

Ligation of one ureter in the human.—It is possible that a similar mechanism is present in the human. Ligation of one ureter has been performed many times either accidentally or as a premeditated move designed to stop urinary flow from that particular kidney. [In my opinion this is very rarely justifiable.] If the kidney is normal there is a transient rise of pressure in the ureter accompanied by some discomfort in the loin lasting a day or two, then secretion stops and atrophy occurs in about two weeks, corresponding fairly exactly with results in the dog. Renal colic does not occur. Hydronephrosis is only slight and the kidney can be restored to normal function if drained before fourteen days have elapsed. I have no knowledge how long a solitary human kidney can be left obstructed before recovery is no longer possible, but would imagine it must be about the same period judging from the length of time the patient survives. If the kidney is infected when the ureter is ligated then one would imagine that a pyonephrosis would result which would be more or less acute according to the degree of infection. That this is not necessarily the case is very surprising; in fact it has been recommended by Huggins (1943) as a method of diverting urine from the bladder prior to cystectomy, the other ureter being brought out to the skin. In 7 patients on whom he performed this operation a pyonephrosis occurred in the one kidney the urine from which was sterile. Simultaneous obstruction of both ureters results in death in ten to twelve days unless drainage is achieved either by operation or spontaneously by the development of a uretero-cutaneous or uretero-vaginal fistula.

Obstructive Anuria

(I) *Calculus Anuria*

Sometimes in old writings one comes across this term applied to the terminal stages of bilateral renal calculous disease. At the present time we use it to describe the condition of sudden blockage of one or both ureters by calculus. Obviously both healthy kidneys can be simultaneously obstructed or the one functioning kidney be alone affected. I have not encountered an example of bilateral simultaneous obstruction, which I imagine is rare, but all of us can probably recall examples of obstruction of a single functioning kidney by a stone in the ureter. The commonest position for the stone is the upper third, occasionally it is as high as the pelvi-ureteric junction; the next most usual place is the lower third, and the region of the brim of the pelvis the least common. Anuria is seldom quite complete but ureteric colic is the rule and indicates the obstructed side. A palpably enlarged tender kidney is present with unilateral muscular rigidity of the abdominal wall. An X-ray will show the stone in most cases. This type of case is not difficult but it is not always so easy. The occasional case in which pain is not a marked feature, where the kidney is not palpable and where radiology is of little help, may puzzle us. It is here that we must go back to the wisdom of our grandfathers before the days of X-rays. Such cases were familiar to them and they were accustomed to operate upon the side in which the patient had last felt pain, as this was more likely to be the functioning kidney; if the patient was unconscious and so unable to give a history they then exposed the kidney over which muscular rigidity could still be felt.

Here I would like to pay an affectionate tribute to Swift Joly who was senior surgeon to St. Peter's Hospital when I was a resident there, and who demonstrated to me these and other truths about the kidney. One can read his book on stone again and again and still find useful sound teaching.

If the first commandment that a urologist must learn to obey is "make sure the other kidney is present", then the second is surely "never expose a kidney without first doing a cystoscopy". In treating these patients the first move is always cystoscopy and catheterization of the ureter on the affected side to confirm the diagnosis. Indeed, in the treatment of any variety of anuria, one must be absolutely certain from the start that ureteric obstruction can be excluded. This applies especially to patients who have developed anuria following any kind of abdominal or pelvic operation, those who have received sulphonamide in any dosage before developing anuria, and in fact, all those who cannot be proved to have previously had a normal urinary tract.

Having made a definite diagnosis and when considering treatment one must concentrate on saving the patient's life; to do this all that is necessary is to drain the kidney above the obstructing stone.

If, in the process of arranging drainage the calculus can be removed too, all well and good, but additional operations in the presence of obstruction and uræmia are never justifiable. As I have already said, renal decapsulation is quite useless in this kind of anuria. Lumbar sympathetic block will relieve the pain of renal colic but has not, in my experience, any effect on the position of an impacted calculus. Even if the obstruction is relieved by removing the stone from the ureter I think it is better—where obstruction has been present for more than two days—to insert a tube through the uretero-lithotomy opening and pass it up to the renal pelvis. A No. 18/F Harris catheter serves the purpose well and can be removed in about five days; not only does this accelerate the recovery of the kidney but it avoids several days of possible urinary leakage from a ureteric fistula due to the obstructive œdema of the ureter associated with the impacted calculus. If the kidney is to be drained because of obstruction in the lower ureter I prefer a nephrostomy to a pyelostomy because it can be maintained indefinitely with greater certainty.

These cases should be treated during the period of obstruction by limitation of fluid intake to one litre during each period of twenty-four hours; just as in the case of non-obstructive anuria, there is a tendency to give too much fluid to the patient. They should, of course, be dealt with as an emergency so that the period of fluid limitation is usually short; when the obstruction is relieved, fluids can be unlimited in quality and quantity because renal function returns very rapidly to normal, and there is no question of loss of concentrating power and loss of chloride in large quantities.

If the ureteric catheter pushes the stone back into the renal pelvis it need not be left in because urine excretion will occur when it is removed and will continue for at least a few days until a formal operation for removal of the stone can be performed under better conditions. A problem arises, however, when the catheter reaches the renal pelvis having passed the obstructing calculus. Urine drains freely as long as the catheter remains in the ureter but anuria reappears if it is removed. I have always disliked the indwelling ureteric catheter and have in the past put a time-limit of twenty-four hours on its use because I have found that it may itself, by becoming blocked, become a cause of obstruction. I am now inclined to the view that under these circumstances it is better to remove the stone by immediate open operation, leaving a drain in the ureter. I believe by so doing one can lessen the period during which the kidney is under stress and thus shorten the time of recovery and hospitalization.

We have recently been confronted by a patient with a second attack of calculus anuria eighteen months after the first. He was known to have a single functioning kidney embedded in scar tissue from two previous lithotomy operations and containing a group of stones in a dilated lower calyx. Impaction of the second stone occurred at the same place as the first—in the pelvic portion of the ureter. Such circumstances demanded a transperitoneal approach to the ureter; extraperitoneally, using the classical approach, one would have been confronted by scarring from the former operation, transperitoneally the ureter with its impacted stone was easily seen and felt. It is an approach which might, I think, be used more often in less exacting conditions than those associated with calculus anuria.

So-called "reflex anuria" does not, I believe, exist. When associated with impaction of a calculus in one ureter, the other kidney and ureter being healthy, it is either the result of excessive fluid loss caused by vomiting or due to a fall of blood pressure following ureteric colic. Acute pyelonephritis also accounts for some of the cases where the other kidney is not entirely healthy which have been given this label in the past.

Slides were then shown which illustrated these points.

(2) *Sulphonamide Anuria*

This condition does not seem to decrease in frequency as one would expect. I would emphasize that in a certain combination of circumstances the use of sulphonamide can be dangerous, especially in children. When a patient has a raised temperature combined with a degree of dehydration such as occurs after repeated vomiting, then the stage is set for trouble, particularly when the fluid loss by the skin is large. Presumably the concentration of sulphonamide in the renal tubules reaches toxic levels and epithelial necrosis occurs. I am not a supporter of the hypothesis that the damage is caused by crystallization of the acetylated compound with resultant blockage of the tubules by crystals. In my experience it has been extremely difficult to find any crystals at all—let alone sulphonamide crystals—in the urine obtained from bladder, ureter or renal pelvis. The familiar brown sandy deposit which has been described as collections of crystals is composed of epithelial cells from the renal tubules singly, in groups, or in the form of casts, together with red cells and the occasional white cell intermingled in varying numbers. We have been particularly interested in this point and have examined specimens by direct film and after centrifuging the urine immediately after relieving the obstruction by ureteric catheter, and in no case has a sulphonamide crystal been found although the specific reaction for sulphonamide in solution is strongly positive. This has made me believe that the sulphonamide ureteric obstruction and the sulphonamide tubular necrosis are really differing degrees of a process which involves destruction and desquamation of renal tubular epithelium.

Recently we have had to consider the case of a woman of 24 years who was admitted to hospital with a diagnosis of acute appendicitis. On admission this diagnosis was doubtful but pelvic peritonitis was certainly present so operation was performed and a fallopian tube distended with pus was removed. By confusion of tablets and grammes, of which this is not a unique example, the patient was then

given exactly double the usual dose of sulphadiazine—4 grammes immediately and 2 grammes every four hours. She did not have more than 2,250 ml. of fluid daily. First hæmaturia and then anuria developed, accompanied by pain in the left loin and renal enlargement. Blockage of the lower ureters was found on cystoscopy and was relieved by immediate ureteric catheterization; a free flow of urine was obtained for a short while but was followed by the passage of only very small amounts. There was no pain in the loins and the kidneys were not palpable. The blood urea rose steadily and there was the usual rise in the blood potassium and fall in the bicarbonate associated with acute renal failure. Treatment by protein, electrolyte and fluid limitation was started. Diuresis began on the seventh morning and the patient passed 15½ litres of urine in the next twenty-four hours.

This case demonstrates that both ureteric blockage and the lower nephron syndrome can occur in the same patient as a result of sulphonamide treatment and goes some way towards confirming my view that these conditions are one and the same but of differing degree.

It should be said in passing that in sulphonamide ureteric blockage it is occasionally necessary to unblock the ureters at a second sitting and I have met one case when even this was inadequate and operative drainage of the renal pelvis by pyelostomy was necessary. I prefer to unblock the ureters by introducing the ureteric catheter repeatedly into the orifice so that the debris comes out like removing a cork from a bottle. If this can be done ureteric catheters need not be left indwelling, though this may occasionally be necessary for a few hours if the condition is of long standing and the orifices very œdematous. In the young female child access to the lower ureters is easy through a child's catheterizing cystoscope, but in the male child it may be necessary to introduce the instrument through a perineal urethrostomy. I have twice had to do this and have found that the wounds heal rapidly and completely in the same way as they do after transurethral resection of the prostate by this route.

(3) *Obstruction Resulting from Debris from Renal Infection*

We have had 3 examples during the past 6 months of obstruction of a solitary ureter by inflammatory debris—all easily relieved by ureteric catheterization.

(4) *Mechanical Ureteric Blockage*

There remain to be considered those cases of anuria due to blockage of the ureters by pressure from outside their walls. After pelvic operations, for example both hysterectomy and colporrhaphy, obstruction of one or both ureters may be found. To obstruct both ureters at one of these operations a surgeon must certainly be grossly unlucky but to say that it might happen is to say that it has happened, thus confronting us with a problem of extreme interest. It is unusual for the urologist to see the case until at least forty-eight hours have elapsed. Cystoscopy will then confirm the obstruction in the lower ureters and one has to make the decision whether to approach the site of obstruction and attempt its relief, or whether it is better to drain a kidney. I have no doubt in my mind that one should avoid the site of the previous operation altogether and simply perform pyelostomy or nephrostomy—preferably the latter. One must remember that one's duty is to relieve obstruction as quickly and as certainly as possible and that this cannot easily be done by trying to find a damaged ureter in a recent operation wound; besides, the operation may be otherwise excellent and it is for that reason undesirable to interfere with it. It is better to expose the lower ureter two or three weeks later when renal function is once more normal, and to divide it adjacent to the constriction then reimplant it into the bladder.

The type of anuria due to blockage of both ureters by extensive spreading carcinoma usually originating in the cervix or vulva comes into another category. Here anuria usually occurs suddenly, but the disease has been slowly progressive for a long time. Treatment of the carcinoma at this stage is usually impossible because growth has already extended beyond the glands at the pelvic brim. I am convinced that it is often better not to drain these kidneys but to allow the patient to die quietly and comfortably of uræmic coma; if there is some chance of curing the patient of the carcinoma then, of course, renal drainage is necessary.

REFERENCES

CAULK, J. R. (1925) *J. Urol.*, **13**, 265.
HINMAN, F. and MORISON, D. M. (1923) *Trans. Amer. Ass. gen.-urin. Surg.*, **16**, 7.
HUGGINS, C. (1943) *J. Urol.*, **50**, 657.

Mr. G. J. Sophian: *Pathogenesis of Anuria*

Renal reflexes.—The study of renal reflexes is based on the concept that the kidney is a "neurile" organ. The word is coined by De Muylder (1952) to convey its essential nervous make-up. Correlating his own researches with those of Van Gertruden and others, he has shown that the neural crest at its caudal tip fuses with the renal anlage in the development of the kidney. He attributes to this fact a considerable nervous sensibility of the organ, a power to sense its environment meticulously and to respond with alacrity in consequence.

This essential physiological trait rises to pathological dimensions in various renal states, particularly anuria. Homer Smith has shown that the salmon and the eel rely on their kidneys for excretory function whilst they are in a fresh-water environment, but this function immediately comes to an end and the gills take over on their transfer to salt water. This phenomenon cannot be explained unless a nervous switchover is envisaged. Bykov (1947), in a large series of dog experiments, elicited the fact

that antidiuresis—previously conditioned—could be evoked in subsequently hypophysectomized animals. In other words, these trained or conditioned animals, when suffering from well-marked diabetes insipidus could exhibit a profound control of their diuresis when transferred to the special experimental platform. One requisite was essential—that the kidneys were not denervated. The supreme importance of the glomerulus in water excretion cannot be contradicted, as in the absence of antidiuretic hormone water retention was perfectly possible and that by nervous control alone.

By stimulation of the fore-brain in the cat Hoff and his team (1951) have succeeded in shutting down the cortex of the kidney and opening up the medullary pathway. By these methods of producing diversion of the renal blood flow he has succeeded in producing lower nephron nephrosis, the acute tubular necrosis of modern nomenclature. Again here such changes were impossible of production if the renal nerves were divided.

The mechanism of the shut-down has been illustrated in sheep, in dogs, in cats, and in rabbits. In addition to the work of the Oxford team of Trueta, Louvgren (1951) of Lund has also shown this pattern of renal blood-flow diversion in a large series of cats. His subjects, under general anæsthesia, were prepared by the insertion of a polythene tube, via the external carotid, down the aorta to the level of the origin of the renal vessels, and they had their abdominal walls infiltrated with a local anæsthetic at the same time. To the exposed end of the polythene tube was attached a bulb of Indian ink. Two hours later after the bulb was squeezed the kidneys were hurriedly removed. In one series the animals were subjected to the prolonged barking of dogs immediately previous to the injection of the ink. The slides demonstrate the difference in pattern of the renal blood flow in the two sets. Here we have proof, which is irrefutable, of the occurrence of the Trueta shunt under absolutely physiological conditions.

Franklin *et al.* (1951) have produced the Oxford shunt with suppression of urinary excretion by short-lived anoxia, provided the renal nerves were intact. He and I (Sophian, 1951), by stimulating the renal nerves electrically, have produced acute tubular necrosis in its various stages. We have also shown that both dioxan and mercuric chloride are responsible for marked diversion of the renal blood flow away from the cortex. Both these substances are responsible for unmistakable and usually fatal acute tubular necrosis. Denervation of one kidney, when minimal dosage of dioxan is employed, shows that it does not respond by cortical shut-down. The utero-renal reflex also evokes diversion of the cortical blood flow. All these help to uncover a nervous responsiveness of the kidney evidenced by a diversion of the renal blood flow under experimental conditions.

The pathologist has illustrated renal blood flow diversion by showing that the subcapsular and the juxta medullary nephrons survive while cortical ischæmia and medullary congestion are accompaniments in acute tubular necrosis. I would cite Shaw Dunn and Montgomery (1941), Sheehan (1951), Solymoss (1949), De and Sengupta (1951) and Telford Govan and MacGillivray in this connexion. Jean Oliver (1951) has shown by his nephron dissections that cortical ischæmia is the underlying change in his anuric material, some of which were Shaw Dunn's original kidneys in which renal blood diversion was quite obvious. Oliver's dissections have also shown that recovery is possible in the ischæmic kidney, but only if the damage has not reached an irreversible state.

Can there be much doubt in face of all this evidence that a vascular shut-down, which can and does open up, underlies the process? In anuria the cortical nephrons are largely devoid of a blood supply; hence there is no cortical urine production. The juxtamedullary nephrons at many stages continue to be supplied with blood. Because of the approximate size of their afferent and efferent glomerular vessels and the large medullary lake—the vasa recta—behind them they cannot maintain a sufficient glomerular pressure adequate for filtration, and hence a possible explanation for anuria is provided.

Clinically the very sudden immediate onset of anuria subsequent on incompatible transfusion could only be explained by a spasmodic, nervously initiated renal shut-down. Less acute shut-downs are heralded by oliguria which is to be expected. The changes of the *milieu intérieur* arising from the renal failure will in themselves cause the shut-down to continue as the kidney is sensitive to its environment, e.g. hypochloræmic anuria. The theoretical production of renal vaso-pressor substances, renin, V.E.M. (vaso-excitor motor substance), will also contribute to its continuation. The treatments of Darmady and Bull are largely applied to minimizing the vicious circle change in the milieu. Valiery-Radot, by exchange transfusion, provides a fresh, balanced cellular environment free from renal vaso-pressor substances which appear to relieve the ischæmic spasm. Peritoneal and intestinal dialysis in correcting the *milieu intérieur* encourage the kidney to function once again.

These are oblique methods for attacking the underlying spasm. A direct attack by anæsthetic denervation of the kidney is far to be preferred. Derot (1952) profitably employs intravenous anæsthetics in the early stage of anuria. Hingson and Lull (1945) in America and O'Sullivan and Spitzer (1946) have had most encouraging and dramatic results with conduction anæsthesia. Naturally the earlier its institution the better but I consider the method has value even in late stages of a continuing spasm as obvious directions of the healing process give grounds for hoping. Two vital precautions are needed in its exhibition. The failure to observe these has led to the abandonment of the method. The injection must be extradural. This largely but not invariably protects against fatal acute hypotension. The anæsthetist must be on the alert immediately to correct it should it supervene, by the simple measure of elevating the legs.

REFERENCES

BYKOV, K. M. (1947) The Cerebral Cortex and the Internal Organs. (Russian translation.) Leningrad.
DE, S. N., and SENGUPTA, K. P. (1951) *Lancet*, ii, 1100.
DE MUYLDER, C. G. (1952) The Neurility of the Kidney. Oxford.
DEROT, M. (1952) Personal Communication.
DUNN, J. S., and MONTGOMERY, G. L. (1941) *J. Path. Bact.*, **52**, 1.
FRANKLIN, K. J., MCGEE, L. E., and ULLMAN, E. A. (1951) *J. Physiol.*, **112**, 43.
GOVAN, A. D. T., and MACGILLIVRAY, I. (1951) Personal communications.
HINGSON, R. A., and LULL, C. B. (1945) Control of Pain in Childbirth. Philadelphia. Also personal communication.
HOFF, E. C., KELL, J. F., jun., HASTINGS, N., SHOLES, D. M., and GRAY, E. H. (1951) *J. Neurophysiol.*, **14**, 317.
LOUVGREN, K. Cited by K. J. Franklin at the International Symposium on Circulation, Ciba Foundation (1951). Also personal communication.
MACGILLIVRAY, I. (1951) *J. Obstet. Gynæc.*, **58**, 92.
OLIVER, J. (1951) *J. clin. Invest.*, **30**, 1305.
O'SULLIVAN, J. V., and SPITZER, W. (1946) *J. Obstet. Gynæc.*, **53**, 158.
SHEEHAN, H. (1951) *Proc. R. Soc. Med.*, **44**, 399 (not fully reported).
SOLYMOSS, A. (1949) *Lancet*, i, 957.
SOPHIAN, G. J. (1951) *Proc. R. Soc. Med.*, **44**, 401.

Mr. R. H. Paramore said that his opinion differed greatly from those of the preceding speakers.

Cases of anuria were primarily obstructive. The obstruction occurred in the medulla: was due to compression of the kidney. There were many hairpin bends in the medulla of the kidney. The obstruction in pregnancy resulted from an exaggerated activity of the abdominal wall muscles: it showed itself especially when these muscles were rendered more tense—as in concealed accidental hæmorrhage. Anuria occurred in the non-pregnant: cases associated with vomiting had been mentioned. Years ago he had published a small volume with the sub-title "Vomiting as a Pathological Force" (Paramore, 1923); but no one had given it any attention. The retching, the straining and the persistent vomiting were thought to have no effect on the individual: people could die from vomiting alone—as in arsenical poisoning!

As a result of the obstruction in the medulla, the convoluted tubules and Bowman's capsules became more and more distended, compressing the capillaries serving them with blood, rendering the flow of this blood more and more difficult, ultimately stopping it. Two events followed. The cells affected suffered degeneration and necrosis: and the blood entering the kidney was forced into the juxtamedullary cortex and parts of the medulla. When the cortex could not further expand, the medulla became squeezed into the pelvis of the kidney. Thus, even when the compression of the kidney was relieved, the pressure of this blood, entering the medulla, might, and often did, maintain the obstruction.

He had treated cases by inducing spinal analgesia. This causes a temporary paralysis of the abdominal wall muscles, relieving the renal compression, and a great fall of blood pressure, which reduces the flow of blood into the kidney. It had been said that spinal analgesia, if it acts at all, acts by causing vasodilatation of renal arterioles, thought to have been constricted, the assumed cause of the ischæmia. This did not explain the limitation of the ischæmia to the outer tracts of the cortex and the flooding of the medulla. Spinal analgesia induces a state comparable with shock: in shock it was believed that arterioles become constricted: thus, if spinal analgesia has any effect on the blood supply to the kidney, it would seem to reduce that supply, helping to explain its beneficial effects. Venesection might also be necessary, especially in post-partum cases in which the blood loss at the birth had been small. From the onset of the disease, the volume of the blood was tending to augment; and the body was doing all it could to get rid of the excess—by causing a dilatation of renal arterioles! But unless urine could escape, this simply served to maintain the medullary congestion: and the vicious circle.

Certain adjuncts were necessary to this treatment. The patient should be made to lie in bed continuously well over on one side: the foot of the bed should be kept raised: starvation should be complete: and only a minimum of water allowed—one pint a day, in sips, sufficing. A case was mentioned (Hayes and Paramore, 1935). If the treatment were tried early enough and more than one spinal injection made—say eight-hourly—the result would be excellent.

REFERENCES

HAYES, D. S., and PARAMORE, R. H. (1935) *Lancet*, ii, 554.
PARAMORE, R. H. (1923) The Toxæmia of Acute Intestinal Obstruction or Vomiting as a Pathological Force. London.

Mr. A. I. L. Maitland asked if some guidance could be given as to the treatment of potassium deficiency.

Mr. Alex Roche said that if one could be certain that one was not dealing with an obstructive calculus, then a pathologist should be called in, though what a pathologist would do he did not know.

Mr. H. Guerrier said that he had read (Van Itallie, T. B., *et al.*, 1952, *Arch. int. Med.*, 89, 353) about calory providers. He referred to the use of emulsion of fat intravenously and asked if it was available in this country, and if information could be given as to its use.

Mr. A. W. Badenoch said that the question had been raised as to how long kidney function could be completely suppressed by a stone impacted in the ureter and its function still return after removal of this stone, provided the other kidney was perfectly normal. Mr. Miller had indicated that the accepted period was three weeks; but three years ago he had had a patient who had a non-functioning kidney from a ureteric calculus five weeks after an attack of colic and the removal of the stone had been followed by functioning of the kidney as shown by leakage from the wound, on the fourth day.

Recently, he had dealt with a patient who appeared to have a non-functioning kidney for at least two months. A uric-acid stone was removed from the ureter and on the fifth day after the removal the patient had an attack of colic and passed a smaller stone. A subsequent intravenous pyelogram showed the kidney function to have returned to normal. In neither of these cases could it be proved that there was no function all the time, but he felt that a kidney should not be condemned because it no longer functioned after an obstruction had been present for longer than three weeks. In such a case, a stone should be removed, although there was presumptive evidence that it had been present for many weeks, with a reasonable hope that kidney function might return.

The President said that Dr. Darmady had told them of the effect on the kidney of prolonged occlusion of the pedicle. Could he state what the time limit was for clamping a pedicle without causing irreversible renal damage? This was important in view of the present day scope of partial nephrectomy.

One variety of obstructive anuria had not been mentioned by Mr. Miller; that due to a tuberculous stricture in the ureter of a solitary kidney. This was not always associated with pain and the anuria might therefore be mistakenly attributed to renal failure due to tuberculous involvement of the remaining kidney.

Mr. Ashton Miller, in reply, said that a plea had been made for a retention of the term "reflex anuria". Before that was invented, "catheter shock" was used. They should get away from the idea that there was a nervous reflex pathway between the ureter on one side and the kidney on the other side. No one, so far as he knew, had ever proved that there was and so the term created a wrong impression.

On the question of increased stress resulting from catheterization of the ureters, he agreed that this was bound to occur, but it was a tragedy to have treated a patient as having a non-obstructive anuria and then to find an obstruction at the autopsy.

Mr. Badenoch had spoken about kidneys recovering after a long period of obstruction. Might it not be that the obstruction was incomplete? When a stone is impacted in the ureter usually the block is not quite complete and a little urine is able to pass.

With obstructions due to carcinoma, anuria comes quite suddenly. For that reason it is very difficult to diagnose, and the tuberculous ones come into the most difficult category.

Professor G. M. Bull replying to Mr. Sophian agreed that the kidney was a neurile organ and reflex changes could occur in its circulation. Splanchnic block might be an effective treatment during the onset phase when this treatment was not contra-indicated by other factors in the clinical picture. Once, however, anuria had been present for six or more hours it was useless. Internal obstruction due to increased intrarenal pressure might be a factor in causing the anuria, but conclusive evidence of this was lacking. Decapsulation of the kidney did not appear to affect the course of the disease.

Potassium deficiency tended to occur during the early diuretic phase. While patients were anuric, his practice was to continue to feed them with a mineral-free diet and to continue it for two days after 1 litre of urine has been passed. The diet was then changed from being mineral-free to one which contained fruit or some other sort of potassium. Administration of potassium chloride was sometimes indicated and was best given by mouth in doses of 5 grammes per day. Even at this level of intake a careful watch should be kept on the serum potassium because of the danger of a swing to hyperpotassæmia.

Professor Bull said that he did not know whether the material mentioned by Dr. Guerrier was available in this country. For intravenous fluid he used a solution of glucose (up to 40%) given through an intravenous polythene catheter. It had been said that 100 grammes of glucose was sufficient to produce maximum suppression of protein breakdown but greater doses were given in order to retain potassium in the cells.

Dr. E. M. Darmady re-showed two slides to elucidate points which had been raised by Mr. Paramore. He said that from the histological point of view and from dissection of the nephron there was no evidence of obstruction occurring in the nephron, and further that histological process and dissection showed that the convoluted tubules and Bowman's capsules were, in fact, not distended. He added that the question of anoxia was a difficult one, but, as he had previously stated as a result of animal experiments, he thought that a period of anoxia lasting from six to eight hours might be sufficient to cause irreversible damage in the human.

Section of Pædiatrics

President—A. G. WATKINS, M.A., F.R.C.P.

[*May* 23, 1952]

Congenital Toxoplasmosis.—G. H. VALENTINE, M.R.C.P., D.C.H.

M. H., aged 2 years 11 months. The 9th child of a family of 10, the eldest 18, the youngest 2. One child died aged 6 of acute gastro-enteritis but all others are well. The father is well. The mother has never been ill and was perfectly well during the relevant pregnancy.

M. H. was born as a normal delivery. Birth-weight 7½ lb. From birth head noted to be large and eyes abnormal. Apart from defective vision development had been normal and intellect good. Aged 2 years 5 months had varicella. Then started to hold head and have headaches. Headaches became more severe with attacks of vomiting. Admitted to North Cambridgeshire Hospital, Wisbech.

Examination.—A lively alert boy. Mental age in normal range. Moderate symmetrical enlargement of head. "Right microphthalmos. Blue-grey iris with evidence of past iritis. Marked vitreous opacity. Retina not seen. Left eye normal size. Iris brown. Lens and vitreous clear. Extensive area of chorio-retinitis between 8 and 10 o'clock extending from retinal periphery to within short distance of optic disc. Slight papillœdema" (Dr. Michael Barling). No other abnormality found.

Tentative diagnosis of toxoplasmosis made.

Investigations: Cerebrospinal fluid on admission: 200 lymphocytes, 60 polymorphs per c.mm. Protein 50, chlorides 748 and sugar 71 mg.%. Culture sterile. Wassermann negative.

X-ray skull, no calcification seen in brain. X-ray chest normal. Blood count normal. Wassermann negative.

Serological investigations on M. H. and family (University of Sheffield Departments of Child Health and Bacteriology, Dr. John Lorber and Dr. J. Beverley):

	Age	Dye test	Compl.-fixation test
M. H.	2 years 11 months	1/460	1/160
	5 days later	1/580	?1/40
Sister	16	1/22	Neg.
Sister	15	Neg.	Neg.
Brother	12	Neg.	Neg.
Sister	11	1/21	Neg.
Brother	7	1/38	Neg.
Brother	4	Neg.	Neg.
Brother	2	Neg.	Neg.
Father		1/70	1/8
Mother		1/250	Anti-complementary
Brother X	18	In Navy.	No tests yet available.

Patient's cutaneous toxoplasmin test strongly positive.

EEG report suggests extensive area of damage in left occipito-parietal region.

Although varying, the C.S.F. cell count remained raised and there was persistent slight xanthochromia. Intracerebral inoculation of animals and repeated examinations failed to show toxoplasma.

There seemed to be no doubt that this was a case of toxoplasmosis of congenital origin presenting the typical features. The raised C.S.F. cell count, the fact that the dye test titre had risen during observation and the more recent acute symptoms suggested that the infection was still active. An attempt at treatment was made with 4:4′-diamidino αω diphenoxypentane di (β hydroxyethanesulphonate)—Pentamidine Isethionate. 50 mg. were given daily for fourteen days. A rest period of fourteen days followed. A further course of 100 mg. daily for fourteen days was then given. At the date of the meeting he was in the middle of the second course.

Addendum

The headaches and vomiting continued intermittently, and twelve days after he was shown at the meeting the vomiting became very severe and death rapidly ensued.

Post-mortem examination.—There was no macroscopic abnormality except in the brain and eyes. There was a gross internal non-communicating hydrocephalus. The aqueduct of Sylvius was completely blocked with inflammatory exudate and there was much exudate and fibrosis around the 4th ventricle. The ependymal lining of the ventricles appeared normal. An enormous subcortical cyst without capsule and lined only by compressed white matter extended from the occipital pole forward as far as the precentral gyrus on the left side. The cyst had ruptured into the left ventricle at its anterior and posterior limits. In the tip of the temporal pole was a cherry-sized cyst with a brown-stained surround. In the centre of this cyst was a calcified area about 2 mm. in diameter. There were several areas of brown staining over the cortex and the brain-stem, suggestive of past hæmorrhages. A recent hæmorrhage around the pons appeared to be the cause of death.

Histological report (Dr. J. C. Valentine).—The material was fixed in formol-saline followed by corrosive formol-saline:

Areas sectioned: Medial surface of frontal cortex. Edge of cyst in temporal lobe. Cerebellar cortex. Aqueduct and surrounding brain. 4th ventricle. Cerebral peduncle. Red nucleus. Lateral ventricle and choroid plexus. Lung. Liver. Kidney. Myocardium.

All sections of the brain tissue in which the surface was included showed a similar picture. There was a slight exudate into the pia arachnoid with occasional small areas of hæmorrhage. The cells of the exudate were for the most part large mononuclears of phagocytic type which contained cytoplasm granules giving a positive Prussian blue reaction and also staining red with Periodic-Acid-Schiff. Some of these cells also contained material which stained very strongly with hæmatoxylin, and this was presumed to be calcium.

In addition to these cells there were a few lymphocytes and an occasional polymorph. Generally the underlying brain showed no striking abnormality.

In the region of the aqueduct there was a very considerable gliosis and the lumen of the aqueduct was reduced thereby to a number of separate channels. These channels held large masses of phagocytic cells similar to those mentioned above. There was no active inflammatory exudate in or around the aqueduct.

In the lateral ventricle the ependyma was present only in a few places. The brain tissue immediately surrounding the ventricles showed an increase of microglial cells.

The edge of the cyst in the temporal lobe showed complete atrophy of the brain and replacement by phagocytic cells containing iron and calcium.

In the white matter of the cerebellum a group of four ovoid bodies was found. In an azure-eosin section they had a dark blue centre and a paler blue cytoplasm. I believe these are toxoplasmic parasites. They correspond well with the published descriptions and illustrations.

The choroid plexus showed remarkably little abnormality.

A section of the 4th ventricle showed that there had been a herniation of a small portion of cerebellar cortex into it.

In none of the sections were any localized areas of necrosis or exudate found within the brain substance. Apart from the four bodies mentioned no parasites were seen and none of the typical pseudo-cysts could be found despite a prolonged search.

There were in the arachnoid exudate many small bodies which might possibly have been parasites but in the presence of so much hæmosiderin and nuclear debris one must be cautious in accepting them as parasites.

Liver: There was a moderate infiltration by polymorphs of many of the portal areas and advanced fatty change.

Kidney: Small collections of lymphocytes were found lying between the collecting tubules. Otherwise the appearance was normal.

Myocardium: Small collections of lymphocytes and mast cells in excess were found around many of the larger blood vessels.

Lung: There was a purulent bronchopneumonia.

No parasites were seen in either the liver, kidney, lung or myocardium.

CONCLUSION.—This may well be a case of toxoplasmic meningitis which had largely healed. There was very little active reaction, and apart from the four bodies highly suggestive of parasites no direct evidence as to the cause of the meningitis was found.

Chorea and Epilepsy.—J. J. KEMPTON, M.D., M.R.C.P.

S. J., girl, aged 7 years.

History.—Patient is the only child of healthy parents. Her birth was normal. She had pertussis at 10 months, and during this illness had one brief period of unconsciousness following a paroxysm. At 15 months she had three convulsions in one day, followed by a short period of pyrexia. At 3 years she had an obscure illness in which she was in bed for a week. Her temperature was raised and she seemed confused and inco-ordinated and was unable to feed herself. It was thought that there was a transient strabismus.

She was first seen at the Royal Berkshire Hospital at the age of 4, with a six months' history of frequent minor fits. These were observed on many occasions and were characteristic attacks of *petit mal*. Physical examination at this time was negative, and her development and intelligence were normal. Tridione was started and, after a few months, major fits commenced, the minor ones having only been slightly reduced in number by Tridione 0·6 gramme daily. Epanutin was added, and after a few weeks on this (¾ grain daily) ataxia and dysarthria became apparent and she was admitted to hospital.

On admission, all anti-convulsant therapy was stopped and the symptoms and signs thought to be due to hydantoin poisoning rapidly cleared up. For a week after admission there were no fits, but after this major and minor fits recommenced. At the time of her discharge from hospital in October 1950, she was an intelligent, co-operative child, though rather emotionally unstable. There were no abnormal physical signs. Following this, anticonvulsant therapy in almost every possible combination was tried for varying periods, none producing any real improvement, and both major and minor fits continued.

In February 1951 abnormal tongue movements, together with hypotonia and abnormal movements of the right arm and hand, suggesting chorea, appeared for the first time. These choreic manifestations became much more marked during the next six months, with salivation and severe and increasing dysarthria. A period of complete rest for three months and aspirin produced no improvement. No anti-convulsant therapy has been given during the last six months.

The present picture is that of severe chronic chorea, and minor and major epilepsy. There is severe inco-ordination and ataxia with hypotonic limbs and "pendulum" tendon reflexes, constant salivation and choreic tongue movements. Minor fits occur with varying frequency and are of brief duration, two or three can frequently be observed within half an hour. Major fits occur at irregular intervals—about once a week. It would seem impossible to assess the mental state. There has been some unavoidable head bruising and the effects of this may contribute to the total picture.

The illness has not been significantly affected by rest, aspirin or any anti-convulsant therapy. Its course has seemed to be slowly progressive until about nine months ago, since when it has remained stationary until the last few weeks during which there has been some improvement.

She has been seen on several occasions by Dr. Ritchie Russell at Oxford, and also at the National Hospital, Queen Square, by Dr. Macdonald Critchley, to both of whom I am grateful for their interest and help.

COMMENT

In the discussion the possibility of some degenerative disease in the nature of Huntington's chorea was considered, but thought to be unlikely. It seemed most probable that this was a case of Sydenham's chorea, occurring in a child with epilepsy. The importance of further investigation and particularly of electroencephalography was emphasized.

Choroidoretinal and Cerebral Defect with Agenesis of the Corpus Callosum.—P. R. EVANS, F.R.C.P.

Female, aged 1 year, the first child of healthy non-consanguineous parents. Normal pregnancy; difficult forceps delivery, and brief period of asphyxia.

The child was well until 2 months old when she had convulsions, doubling herself up and looking downwards and to the right. At 10 weeks she was admitted to hospital under the care of Dr. P. L. Pickering and later Dr. Victoria Smallpeice. C.S.F. contained 55 R.B.C., 84 lymphos., 20 polys., protein 60 mg.%. Pandy test positive; chlorides 690 mg.%, reduced blood sugar; W.R. was negative and Lange 000000000. One month later C.S.F. was normal except for protein 56 mg.%, and it is now completely normal. Blood W.R. and Kahn were negative. The discs were pale and the fundi showed many patches of choroidoretinal atrophy, later considerable pigmentation surrounded the atrophic areas. The maculæ were involved. Mantoux 1/1,000 negative. X-ray: no intracranial calcification. Pneumo-encephalogram showed general dilatation of the ventricles with mural irregularities and agenesis of corpus callosum. EEG showed frequent spiking suggesting at least two epileptogenic foci; one right fronto-parietal and one left inferior parietal. The fits are not controlled by phenobarbitone.

Mental development ceased; even the grasp reflex is absent. There is muscular weakness but the tendon reflexes are normal. The appearance of the eyes suggests toxoplasmosis but complement and dye-fixing tests on mother and child have been negative, and as there are also no intracranial calcifications, this diagnosis cannot be maintained. An alternative would be the "Chorioretinopathy associated with other evidence of cerebral damage in childhood; a syndrome of unknown origin separable from congenital toxoplasmosis", of Sabin and Feldman (1949, 1950). "Agenesis of the corpus callosum" is a radiological diagnosis, and it may be that instead of agenesis there is really destruction of the corpus callosum as well as of other parts of the cerebrum.

REFERENCES

SABIN, A. R., and FELDMAN, H. A. (1949) *J. Pediat.*, **35**, 296.
——, —— (1950) *Amer. J. Dis. Child.*, **79**, 366.

Encephalo-trigeminal Angiomatosis (Sturge-Weber Syndrome) Treated by Removal of the Affected Cerebral Hemisphere.—P. E. POLANI, M.D., M.R.C.P., D.C.H. (Introduced by P. R. EVANS, F.R.C.P.).

Case I.—A. McK., female, aged 6 years. A large left trigeminal nævus was noticed at birth. Right-sided fits started at the age of 3 months. From this age onwards it was noticed that the patient had very little movement in the right side of the body. She sat up at 18 months, babbled at 2 years, and walked at 4 years. In the last year she had had moderately severe temper tantrums and had become difficult to manage. Epileptic fits had continued at the rate of two or three per week in spite of very adequate and varied medication for years.

On examination.—There was a right-sided hemiplegia with slight spasticity. The right limbs were smaller than the left. Right homonymous hemianopia. Sensation (pin-prick only) normal. Her mental age was approximately 2–3 years. She uttered a few single words with poor articulation.

EEG Report (Dr. D. A. Pond).—The record obtained under seconal narcosis showed a very considerable asymmetry. Over the right cerebral hemisphere low-voltage theta activity was seen broken up with bursts of higher-voltage slow waves. Over the left hemisphere there was little electrical activity, and indeed in the inferior A.P. line of electrodes no activity at all was apparent. The record suggested more or less complete absence of function of the left cerebral hemisphere. No spikes or other epileptic features were observed, possibly because the degree of narcosis inhibited them (Fig. 1).

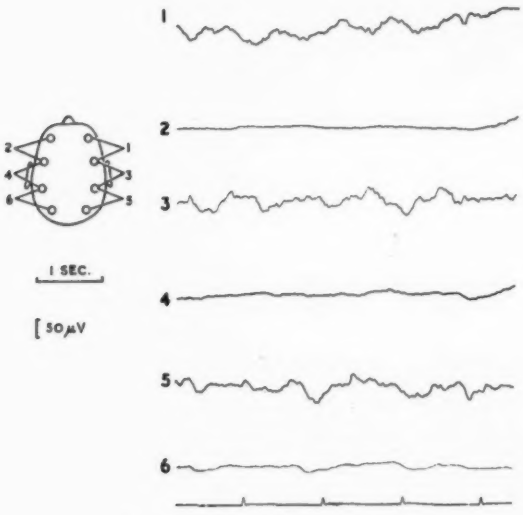


FIG. 1.—EEG of patient A. McK.

X-ray of skull.—The left half of the cranial cavity was smaller than the right. Throughout the left hemisphere there was a widespread "tramlines" pattern of calcified streaks resulting from deposition of calcium in the cortex on either side of the cerebral sulci (Figs. 2 and 3).

Air encephalogram.—The cerebral sulci were well outlined, but no air entered the ventricular system. Over the left hemisphere the subarachnoid spaces were capacious, and the outline of the left cerebral hemisphere, revealed in this way, showed that it was markedly shrunken when compared with the right.

Operation (1.4.52).—Left lateral craniotomy was performed under general anæsthesia (Mr. M. A. Falconer, Guy's—Maudsley Neurosurgical Unit). The whole left hemisphere presented a fairly uniform deep-red colour with a fine diffuse angiomatous network in the pia arachnoid. A left hemispherectomy was performed with preservation of the caudate nucleus and thalamus. The choroid plexus of the left lateral ventricle was also removed (Fig. 4, X-ray of specimen).

Pathological report (Dr. A. L. Woolf): The general impression is of diffuse capillary and venous angiomatosis of the pia with early and progressive degenerative changes in the brain more closely related to œdema than anoxia. There are numerous calcospherites in some parts of the cortex.

FIG. 2.—Left lateral view of skull of patient with Sturge-Weber syndrome, showing extensive parieto-occipital calcifications of "tramline pattern".

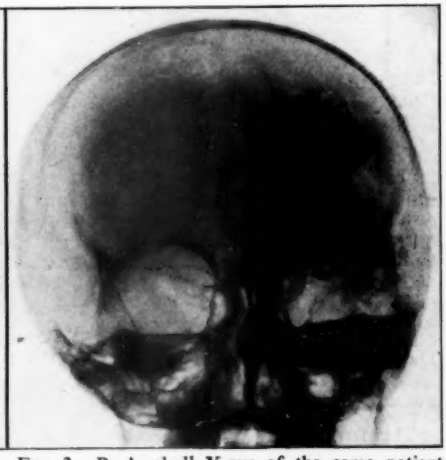


FIG. 3.—P. A. skull X-ray of the same patient showing extensive calcification in the left cerebral hemisphere, asymmetry of the skull with flattening of the left side and rotation around its longitudinal axis, and slight thickening of the left half of the vault.

FIG. 4.—X-ray photograph of the left cerebral hemisphere removed at operation showing the pattern of "calcification" in the cerebral convolutions.

Follow-up (23.5.52).—The patient has had no medication since the operation. She has had neither fits nor tantrums and is much more friendly, sociable and happy. She talks much more and the articulation has improved. She sings in tune, walks without getting tired and runs.

Case II.—R. D., male, aged 4 years. A similar case to A. McK. Hemispherectomy on 15.8.51. Cessation of fits and general improvement comparable to A. McK.'s.

Comments.—Direct surgical approach in the treatment of infantile hemiplegia with fits by excision of cerebral scars has been repeatedly tried but frequently without permanent results. A reason for the poor results may possibly be that operative removal has been too limited and that extensive cerebral pathology still remains in parts of the brain which have not been removed: localized excision, however, may be usefully carried out when cerebral pathology is more limited.

In 1949 the South African neurosurgeon Krynauw described to the Society of British Neurological Surgeons five cases of infantile hemiplegia which had been treated by hemispherectomy. He had tackled his first case in 1945 and considered this extensive operation to be warranted by the widespread pathological and functional damage of the affected hemisphere. The operation of hemispherectomy had previously been undertaken for a cerebral tumour, probably for the first time, by Dandy in 1928 (Dandy, 1928). In 1950 Krynauw published his subsequent results in a paper in which he described 12 cases (Krynauw, 1950).

From Krynauw's cases and from the other cases reported by various authors and amounting to probably two dozen published case reports, one can gather the indications for this operation in congenital hemiplegia. Naturally great caution must be exercised until we know more about the long-term results of the operation. The present view is that when severe infantile hemiplegia is present the operation should be undertaken if (1) there are fits that cannot be controlled with adequate medical treatment, (2) there is a severe behaviour disturbance which interferes with socialization of the patient, and (3) there is intellectual impairment or deterioration.

Severe infantile hemiplegia plus any of these other three criteria—and usually more than one is present—constitutes indication for this operation according to Krynauw (1950) and Cairns and Davidson (1951). Our 2 cases fulfilled all these indications. In addition they showed, as other cases described in the literature, an abnormality of the E.E.G. not only on the side of the affected hemisphere but also on the opposite side.

The post-operative results as described in the literature are most rewarding, although the follow-up studies are necessarily short as yet. This is borne out by these 2 cases. Neither of them has had any fits since operation although neither of them is receiving any medication. There has been no worsening of the hemiplegia: actually they have shown definite improvement: speech has improved in both cases and this neurological aspect apparently need not cause any anxiety post-operatively. The behaviour disturbance has also improved and this has been the rule in all the reported cases. The hemianopia, of course, remains complete, but neither patient is noticeably disturbed by it. It is stated that when this lesion is not present before operation in infantile hemiplegia, its invariable appearance after operation does not worry the patient unduly (Cairns and Davidson, 1951).

In both patients the hemiplegia was associated with meningo-trigeminal angiomatosis. There is only one other case of this type described in the literature in which such treatment was tried (Cairns and Davidson, 1951). It is thought at present that the same indications for hemispherectomy apply to these cases as to the others of infantile hemiplegia (Falconer, 1952). However, this method of treatment seems most rewarding in those patients with the Sturge-Weber syndrome in whom brain pathology on the affected side is very extensive. The prognosis for life if the disease is allowed to run its natural course seems to be bad in such cases (Greenwald and Koota, 1936), and attempts at surgical removal hitherto have been considered "nothing less than foolhardy" (Cushing and Bailey, 1928).

The author is greatly indebted to Dr. P. R. Evans and to Mr. M. A. Falconer for their permission to show these two cases, and to Drs. D. A. Pond and A. L. Woolf for their reports.

REFERENCES

CAIRNS, H., and DAVIDSON, M. A. (1951) *Lancet*, ii, 411.

CUSHING, H. W., and BAILEY, P. (1928) Tumours Arising from the Blood Vessels of the Brain. Springfield.

DANDY, W. E. (1928) *J. Amer. med. Ass.*, **90**, 823.

FALCONER, M. A. (1952) Personal communication.

GREENWALD, H. M., and KOOTA, J. (1936) *Amer. J. Dis. Child.*, **51**, 868.

KRYNAUW, R. A. (1950) *J. Neurol. Neurosurg. Psychiat.*, N.S. **13**, 243.

[*June* 28, 1952]

MEETING HELD AT THE RADCLIFFE INFIRMARY, OXFORD

Tension Cysts of the Lung [*Abstract*].—G. C. LAURIE PILE, F.R.C.S.

In the past three years Mr. Pile had operated on 5 children because of respiratory difficulty arising as a result of rapid increase in size of congenital cysts.

One 6 weeks' old baby died following operation and one case died of respiratory difficulty while awaiting operation. A further 3 cases are still under observation and it is clear that this condition is not as rare as had been supposed.

The ages of the children at operation were: 6 weeks, 9 weeks, 3½ years, 11 years, 13 years.

[Full report will appear elsewhere.]

Experiences with Retrolental Fibroplasia in Oxford

By MARY W. COXON, M.B., D.C.H.

THE following is a brief account of our experience of retrolental fibroplasia in Oxford.

In all, 25 babies born in the United Oxford Hospitals have been known to develop retrolental fibroplasia, and recently 3 cases have been admitted from other hospitals for treatment.

The first example presented itself in the out-patient department in November 1949 as a case of mental defect with gross nystagmus. We referred the child to Mr. A. C. L. Houlton of the Oxford Eye Hospital who provisionally diagnosed retrolental fibroplasia but considered that an eye should be enucleated to exclude retinoblastoma.

By March 1950 7 further cases were seen in the course of a routine follow-up of premature babies. All were in the late stages of the disease and eyes were enucleated from 3 of these to exclude retinoblastoma. Of these 8 early cases, five were blind, 1 retained perception of light in one eye and 2 will probably have useful though defective vision. Nystagmus was a striking feature of all these cases.

In the light of this group Dr. B. A. Bembridge and Mr. C. R. S. Jackson of the Nuffield Laboratory of Ophthalmology, decided to re-examine all accessible specimens of eyes enucleated from young children in the Oxford Eye Hospital. In this way 3 further cases were traced, 1 born in 1947 and 2 in 1948. These had been previously diagnosed as pseudogliomata. No case earlier than 1947 was found.

It was also decided to examine the eyes of all surviving premature babies born in the Oxford Hospitals from 1946 to 1950, weighing 4 lb. and under at birth. 88% of the children were seen either in the out-patient department or in their homes. The fundi were examined ophthalmoscopically, with dilated pupils, either by Dr. Bembridge, Mr. Jackson or myself. No further cases were found and no evidence was seen of retinal scarring or detachment.

In April 1950 a team was formed composed of Mr. A. C. L. Houlton of the Oxford Eye Hospital, Mr. C. R. S. Jackson and Dr. B. A. Bembridge of the Nuffield Laboratory of Ophthalmology and Dr. V. Smallpeice and myself from the Children's Department. It was decided to examine the eyes of all babies weighing 5 lb. and under at birth, before they left hospital, and to keep them under observation for six months after discharge. At a special clinic they were seen monthly for two months and then two monthly until reaching 6 months of age. From early in 1951 and up to the present time infants were seen at weekly intervals while in hospital, the first examination being made as soon after birth as the clinical condition permitted. On leaving hospital they are seen at weekly or fortnightly intervals until 3 months old, then at monthly intervals until 6 months old. Infants showing any abnormality are seen twice weekly, or even daily. All examinations are made under 1% homatropine in 2% cocaine, the child being given a teat to suck. At no time has general anæsthesia been used and on only two occasions has a local anæsthetic been given to permit fixation forceps being used. Dr. Bembridge undertook to section the eyes of all fresh stillbirths and neonatal deaths amongst premature babies in an attempt to elucidate the early pathological changes in the retina.

Prophylactic Vitamin E

In 1949 Owens and Owens published two series of cases, in one of which they claimed that vitamin E given prophylactically, prevented the development of retrolental fibroplasia, and in the second smaller series, that given in the early stages it arrested the disease process. On the evidence of these workers, from April 1950 α-tocopherol acetate, 150 mg. daily, was given to all premature babies from a week after birth to 6 months of age. This regime was continued until March 1951. Over this period

of twelve months, 5 babies developed retrolental fibroplasia and there was no evidence that the severity of the disease was modified in any way. Vitamin E was also given to twins, from 6 months of age, who showed retinal folding and gross nystagmus, but no membrane formation. The disease did not progress and the children will probably have useful vision. The vitamin was not given until a time when the disease process was considered to be waning and the process was probably self-limiting. Of the 5 children with retrolental fibroplasia who received vitamin E from birth, 2 are blind, 1 partially sighted, 1 appeared to have good vision in one eye when last seen at 6 months of age; the fifth child has good vision in one eye but was treated with ACTH in addition, though treatment was started at a time which we would now regard as too late to prevent serious scarring.

Also arising from Owens and Owens' work, it was suggested that excessive use of water-miscible vitamins A and D and iron salts, might be associated with the increased incidence of retrolental fibroplasia. Delayed introduction of iron preparations until the eighth week, in the absence of anæmia, has been practised in Oxford hospitals since 1950.

The Effect of Oxygen Therapy

In considering possible changes in the early care of premature babies which might affect the development of retrolental fibroplasia, one of the most striking appeared to be the increased use of oxygen therapy over the previous five years, and the greatly improved apparatus for administering oxygen. "Oxygenaire" tents were used in the Oxford hospitals and at this time (1950) all babies developing retrolental fibroplasia had been nursed in these tents. It was decided to reduce the amount of oxygen given to premature babies to the minimum necessary to prevent cyanosis. Jackson (1951) repeatedly sampled tents in use at the hospital and found that as used at that time (i.e. the tent with lid closed being flushed with O_2 at a flow of 6 litres per minute for two to three minutes, followed by a flow of 1 litre per minute) there resulted a concentration of 75–80% of oxygen developing rapidly and being maintained until the tent was next opened, usually in about three hours' time. The CO_2 concentration did not rise above 0·01%; the oxygen concentration was considerably reduced by partially opening the tent lid, and it has been our practice since 1950 to nurse all babies in tents with lids open at least ¼ in., the concentration of oxygen being adjusted to between 30 and 40%.

Attempts to produce retrolental fibroplasia in newborn rabbit litters by exposing them to similar oxygen concentrations were unsuccessful. The rabbit was chosen because, anatomically and developmentally, the eye closely resembles that of the human. In 1951 Szewczyk of St. Louis published a paper in which he claimed that excessive oxygen administration or sudden deprivation of oxygen was the cause of retrolental fibroplasia. Retinal changes characteristic of the condition were said to develop immediately on removing the infants from incubators and to be reversed by returning the infant to a high oxygen concentration. Our experiences have not confirmed this. Retinal changes in some cases have occurred seven weeks after discontinuing oxygen in any form and never less than two weeks after the babies have been removed from tents. In 2 cases the infants have been returned to a concentration of 60% of oxygen when early signs of retrolental fibroplasia appeared, but in neither case did the retinal changes retrogress. For the past two years it has been our practice to reduce oxygen gradually.

The Use of ACTH

In November 1950 the first use of ACTH was described by Dr. Richard Day at the Presbyterian Hospital, New York, who gave us details of the cases he had treated. Our next case was diagnosed in November 1950. The child was treated for seventy-two days and a total of over 1 gramme of ACTH was used. We now regard such an extensive course as unnecessary and our recent practice is to give a daily dosage of 20–30 mg., depending on the weight of the child, for fourteen days, and to repeat this course if further progress of the disease occurs.

12 cases have now been treated with ACTH. One child died of gastro-enteritis during a ward epidemic. Control cases were not used, as it was felt unjustifiable to withhold any remedy which might prevent the disastrous consequences of the fully developed disease. While the number of cases is very small the following comparison may be drawn between the 11 cases receiving ACTH, and the preceding 12 consecutive untreated cases. In the untreated cases 7 children are blind, 2 partially sighted, 2 have seriously defective vision with marked nystagmus and 1 retains good vision in one eye. Of the 11 surviving treated cases, no child is blind, but there are two blind eyes in the first 2 children treated. In both these cases, it is now felt that treatment was started too late.

The complications of ACTH therapy seem mainly to be attributable to hospitalization rather than specific effects of the hormone. Hypertension developed during treatment in all cases, reaching alarming heights in 2. In all cases this has been within normal limits six weeks after ACTH has been stopped.

In May 1952 Reese *et al.* and Lamotte *et al.* (1952) published larger series of cases treated with ACTH. Reese concluded that it had no effect on the progress of the disease while Lamotte considered it worthy of further trial.

SUMMARY

In Oxford our present practice is to keep the eyes of all premature babies, weighing 5 lb. or less at birth, under close observation for the first six months of life. Oxygen administration is limited to the minimum necessary to prevent cyanosis; it is reduced gradually, and the concentration of O_2 maintained at 30 and 40%. When retrolental fibroplasia is diagnosed a course of ACTH is given.

REFERENCES

JACKSON, C. R. S. (1951) *Brit. Med. J.*, ii, 1129.

LAMOTTE, WILLIAM D., Jrn., PYNER, GEORGE F., and SCHEIE, HAROLD G. (1952) *Arch. Ophthal.*, **47**, 556.

OWENS, W. C., and OWENS, E. U. (1949) *Amer. J. Ophthal.*, **32**, 1631.

REESE, A. B., BLODI, F. C., LOCKE, JONNE, SILVERMANN, WILLIAM A., and DAY, RICHARD L. (1952) *Arch. Ophthal.*, **47**, 551.

SZEWCZYK, T. S. (1951) *Amer. J. Ophthal.*, **34**, 1649.

The Factor of Inheritance in Convulsive Disorders in Childhood [*Abridged*]

By CHRISTOPHER OUNSTED, D.M., D.C.H.

HIPPOCRATES asserted that an inherited diathesis rendered the scions of epileptic fathers liable to suffer from fits. His views gradually became general in Western Europe, either displacing, or merging with the older concept of demoniacal possession. Boethius reported that the ancient Scots gelded male epileptics and that an affected woman was "kept from all company of men; and if by chance, having some such disease, she were found to be with child, she and her brood were buried alive; and this was done for the common good lest the whole nation should be injured or corrupted". The milder Swedes have forbidden marriage to persons with idiopathic epilepsy since 1757. Similar laws have been made in Germany in this century.

Modern authors have found that a constitutional tendency to suffer from fits is evident not only in epilepsy but also in febrile convulsions (Lennox, 1949), eclampsia (Rosenbaum and Maltby, 1943), anæsthetic convulsions (Williams and Sweet, 1944), convulsions following minor brain injury (Bridge, 1949).

The emphasis placed on the ætiological force of the inherited factor varies widely. This appears to be due in part to selective sampling. Thus, some studies are based on epileptics in institutions, others on epileptics with associated mental deficiency, others on series of dizygous and monozygous twins, and others on patients whose seizures are provoked by fever.

We are trying to learn something about the natural history of convulsive disorders of children in Oxford, and, to that end, we are collecting a fresh series of consecutive cases. The material presented here is a pilot analysis of the family histories of the first 337 children entering the sample.

The nature of the sample.—We have tried to cast our net as widely as possible, and to collect a representative sample of all the convulsive disorders of young children as seen in general practice, in institutions, in the children's wards and out-patient clinics, in infant welfare clinics and as encountered by health visitors.

No selection of cases was made. The occurrence of any sort of convulsive disorder was the sole condition of entry to the series.

Drawing the family tree.—The only relations considered were the full siblings, parents, aunts, uncles and grandparents of the propositi. A history was accepted as positive if a clear history of a fit was obtained; where doubt existed about the nature of the attack the relative was excluded.

The Results

(*a*) *Incidence of positive histories.*—There were 337 children in this sample. 4 of these children were of unknown parentage, and a further 6 were the illegitimate offspring of fathers unknown. There were thus 327 whole family trees and a further 6 half-trees available.

Of the 333 propositi with whole or half-trees, 130 had a kinsman with a clear history of a convulsive disorder. Thus the incidence of children with positive family histories was 39%.

(*b*) *The source of the positive histories.*—Table I shows the source of the positive history in the 130 children with evidence of familial taint. The striking feature of the figures is the disparity of incidence between the maternal (distaff) and the paternal (spear) sides of the family tree; 25% had an affected relative on the distaff side, compared with 9·2% on the spear side. This disparity was seen again when the incidence of convulsive disorders in parents was considered. The incidence of affected mothers was 8·1%, that of affected fathers was 3·1%. In both cases the incidence of the taint was 2½ times greater on the maternal than on the paternal side of the family.

TABLE I.—SOURCE OF POSITIVE FAMILY HISTORIES

Source	Number of cases
Siblings only	23
Spear side only	24
Distaff side only	76
Both spear and distaff	7
Percentage of all cases with taint on spear side	9·2%
Percentage of all cases with taint on distaff side	25%

(*c*) *Incidence in siblings.*—The propositi in this series had 490 siblings born alive. Among these siblings 56 had developed a convulsive disorder of some kind at the time our enquiry was made, giving an incidence of 11·4% of siblings affected. This figure has, of course, only an *ad hoc* significance because many of the siblings were young children and some of them may develop fits in the future.

The influence of a positive family history of fits on the incidence of fits in siblings was examined. In the group with a positive family history the incidence was 16%; in the group with a negative history the incidence was 9%.

(*d*) *The familial taint and the diagnosis.*—Throughout the sample we commonly found different types of convulsive disorders within single families. Epilepsy and febrile convulsions did not segregate from one another. In Table II a comparison is made between the incidence of positive family histories in 100 children whose first fit was a febrile convulsion and in 106 children in whom the first fit was afebrile. In the febrile convulsion group the incidence of positive histories was 41%; in the afebrile group the incidence was 46%.

TABLE II.—FAMILIAL TAINT AND THE NATURE OF THE FIRST FIT

	First seizure febrile (100 cases)	First seizure afebrile (106 cases)
Family history positive	41%	45%
Family history negative	59%	55%

The family trees shown in Figs. 1 and 2 illustrate the manner in which different types of convulsive disorders may appear within single families, and, indeed, in the same patient.

(*e*) *Assortive mating.*—Assortive mating between men and women from families tainted with epilepsy has been suggested as an ætiological factor in convulsive disorders in their offspring, the presence of the taint on both sides enhancing the risk that affected children will be born.

From our figures it was possible to calculate the number of unions with bilateral taint that would be found if mating had occurred in a purely random fashion. When this was done it appeared that, in the absence of assortive mating, we should expect to find 7·8 unions of this type. We did in fact find 7 families with bilateral taint. This close agreement between the theoretical and actual findings suggests that assortive mating was not significant in this series and the suggestion receives further support from the fact that none of the siblings in the 7 families with bilateral taint has yet had a fit.

(*f*) *Prognosis and heredity.*—The work reported by Bridge (1949) from Johns Hopkins Hospital suggests that the presence of the hereditary factor is not necessarily associated with a bad prognosis either in established epilepsy or in febrile convulsions. Our experience accords with this view, but we require a longer follow-up before we can give figures of any real value. Fig. 1 illustrates the way in which a heavily loaded tree may be associated with full recovery in many of those affected.

(*g*) *Heredity and age of onset.*—The histogram in Fig. 3 shows the incidence of positive family histories related to the age at the first fit. Among those children who had their first fit in the 2nd year of life, 60% had positive family histories: when the first fit occurred after the age of 5 years the incidence was only 24%. More detailed figures showed that the incidence rose sharply from birth to reach a peak at about 17 months, and declined thereafter in an exponential fashion as the children approached adolescence.

DISCUSSION

I wish to emphasize that our series is very small and that our analysis is no more than an *ad hoc* pilot survey.

Our results for the incidence of positive family histories agree with those of American workers both for children with epilepsy (Bridge, 1949) and for febrile convulsions (Lennox, 1949). This is, however, a crude and misleading measure of the ætiological force of heredity, particularly in syndromes as common as the convulsive disorders. The incidence in siblings is, on the other hand, quite good evidence that some genetic factor is operative.

Gowers (1901) was, I think, the first to suggest that women more commonly transmitted the epileptic taint; Lennox, Gibbs and Gibbs (1940) have supported this view on the basis of electroencephalographic studies. Our figures show quite a striking tendency for the taint to be manifest on the distaff rather than the spear side: this cannot easily be explained in simple genetic terms.

The curious relationship between the age at the first fit and the incidence of familial taint is usually expressed by saying that "heredity lowers the age of onset of epilepsy". While that statement appears superficially true, reflection shows that it is in fact a tautology. An alternative view is that the inherited factor operates through some transient imbalance of electrochemical maturation, which may be corrected with advancing age. This suggestion would serve to reconcile the association between a positive family history and a relatively good prognosis and it would also explain why surveys which are limited to adult epileptics, such as Alström's (1951), show little evidence of an active hereditary factor, whilst in surveys made on young children the factor is quite prominent.

Finally one major difficulty must be faced. The inherited characters that we are able accurately to study are, of course, of two kinds. They are either fixed qualitative segregating characters such as blood groups and colour-blindness, or quantitative measurable non-segregating characters such as height or intelligence. Characters belonging to the first class may be studied in terms of Mendelian ratios; those of the second class by means of correlation coefficients between measurements.

Much of the genetic work on epilepsy, and all the eugenic laws and practices relating to that syndrome, are based on the tacit assumption that epilepsy is a character of the first class. In practice,

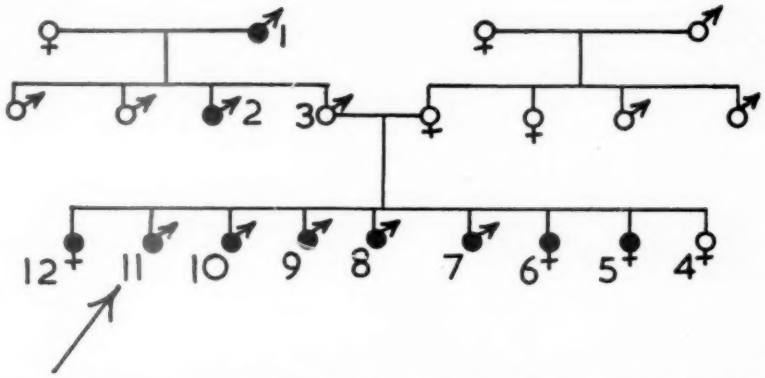


FIG. 1.—1, *Grand mal* epilepsy: died aged 50 after a fit; 2, *grand mal* epilepsy from 3 to 16 years: now aged 56, well; 3, No fits, violent rages; 4, No fits; 5, 6, 7, Isolated febrile convulsions only; 8, Febrile convulsion aged 2½, *grand mal* epilepsy from 3 to 7, now 21 and well; 9, Three *grand mal* seizures in 3rd year of life, now 15 and well; 10, One *grand mal* attack, aged 4; now 13 and well; 11, Propositus: epileptic with psychopathic equivalents; responded to Epanutin with remission lasting two years; 12, *grand mal* epilepsy from 1 to 5; now aged 10 and well.

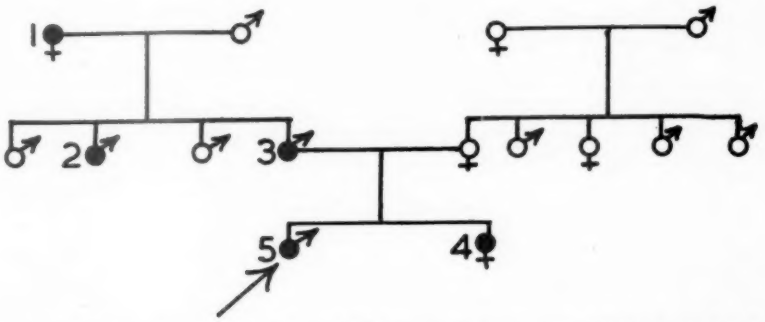


FIG. 2.—1, Senile dementia and fits; died aged 70 in status epilepticus; 2, Life-long *grand mal* epilepsy; died aged 59, during a fit; 3, Adult *petit mal* and violent rages; not responding to treatment; 4, *grand mal* epilepsy for three years, spontaneous remission now lasting five years; 5, Propositus: one febrile convulsion: EEG within normal limits.

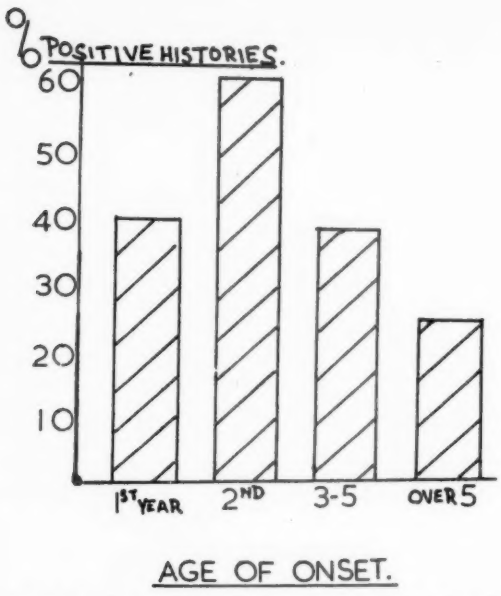


FIG. 3.—Histogram showing the relationship between the age at the time of the first fit and the incidence of positive family histories.

however, the tendency to have fits appears to be a quantitative variable both clinically and in animal experiments. Russell (1950) said succinctly "It is simpler to think of all people as epileptics, and regard the matter as one of threshold". If indeed epilepsy and other convulsive disorders are non-segregating manifestations of quantitative variations in the seizure threshold, then we must discover some method of measuring that threshold in individual patients in order that correlation coefficients may be calculated between series of affected patients and their kinsmen. At present no such measure is available.

I wish to thank Dr. Victoria Smallpeice who supervised and directed this work, and the Research Advisory Sub-Committee of the Oxford Regional Hospital Board for much valuable support.

REFERENCES

ALSTRÖM, C. H. (1950) *Acta psychiat. Kbh.* Supp. LXIII.
BRIDGE, E. M. (1949) Epilepsy and Convulsive Disorders in Children. New York.
GOWERS, W. R. (1901) Epilepsy and Other Chronic Convulsive Disorders. London.
LENNOX, MARGARET A. (1949) *Amer. J. Dis. Child.*, **78**, 868.
LENNOX, W. G., GIBBS, E. L., and GIBBS, F. A. (1940) *Arch. Neurol. Psychiat., Chicago*, **44**, 1155.
ROSENBAUM, M., and MALTBY, G. L. (1943) *Arch. Neurol. Psychiat. Chicago*, **49**, 204.
RUSSELL, W. R. (1950) *Lancet*, i, 258.
WILLIAMS, D., and SWEET, W. H. (1944) *Lancet*, ii, 430.

JOINT MEETING No. 6

Section of Psychiatry with Section of Anæsthetics

Chairman—DESMOND CURRAN, F.R.C.P., D.P.M.
(President of the Section of Psychiatry)

[*June* 10, 1952]

DISCUSSION ON NEW MUSCLE RELAXANTS IN ELECTRIC CONVULSION THERAPY

Dr. Anthony Edridge, *Senior Registrar, Department of Anæsthetics, Westminster Hospital*: In 1934 Meduna introduced convulsion therapy as the treatment of certain mental disorders. The convulsions he initiated with what, from a clinical viewpoint, were overdoses of analeptic agents—*par excellence*, cardiazol.

Two disadvantages of this technique rapidly became apparent. Firstly, that the violence, and perhaps nature, of these convulsions was in many instances sufficient to produce crush injuries and dislocations, especially of the spine, and, secondly, that the prodromal stage of the convulsion was so unpleasant that an appreciable number of patients refused to continue treatment. Thus we find that, from the late 1930's onwards, attempts were being made (*a*) to attenuate the violence of the convulsions (Bennett, 1940, 1941, 1943, and Palmer's 1939, 1946 pioneer work—curare—spinals) and (*b*) to anæsthetize the patient before and through the induction of the convulsion.

In 1938 Cerletti and Bini induced convulsions electrically, and the instantaneous stunning effect of this method, together with the associated retrograde amnesia, obviated almost entirely the (to the patient) major conscious objection to the older technique, i.e. its well-remembered unpleasantness. The objective complications of fracture and dislocation remained, but though the likelihood was accepted as a possibility, the percentage of incidence was so little agreed upon—as the figures in several papers show—that the majority of workers relied on posture and restraint to keep these in check.

It was in 1947 that, consequent on its widespread availability, Hobson and Prescott reported their use of curare in electric convulsion therapy.

Papers on the use of decamethonium iodide (C 10) and gallamine (Flaxedil) followed and two schools of thought were soon apparent: (1) Those who *did* attenuate, using either tubocurarine, gallamine or C 10 with or without a cover of thiopentone, and (2) Those who regarded attenuation as unnecessary and maybe hazardous.

In 1949 Bovet *et al.* drew attention to the paralysant action of the bis-choline esters of succinic acid. He claimed that in animals, these produced paralysis of short duration with an ultra-rapid onset and an equally rapid recession. It is on the use of these during the past year that this paper is based.

The physiologically active (or paralysing) part of the molecule is the cation, a chain at each end of which is a quaternary ammonium group.

These ammonium groups are of two kinds: they may contain 3 methyl (CH_3) groups and are then called methonium, or one of these methyl groups may be substituted by an ethyl (C_2H_5) group and then the term ethonium is used. Thus the whole active cation (bearing in mind that the acid is succinic) may be called suxamethonium or suxethonium.

To these two different but closely related cations may be linked one of the halides, *chlorine*, *bromine* or *iodine* as the anion and thus the possible combinations are, in one group:

Suxamethonium chloride (or succinylcholine)—"Scoline",
Suxamethonium bromide, which we have used as "Brevidil M", and
Suxamethonium iodide, which was one of Bovet's original compounds,—Succinylcholine iodide (S.C.I.);

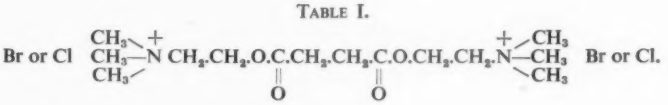
and, in a 2nd group,

Suxethonium chloride,
Suxethonium bromide, which we have used as "Brevidil E", and
Suxethonium iodide, which Bovet called "I.S. 362".

The halide anions are physiologically inert and the three suxamethonium compounds in the body all liberate an identical active cation, as do the three suxethonium compounds. The anions, however, do determine the small differences in the physical properties of the drugs, which may influence our choice for clinical use. All these compounds in aqueous solution undergo slowly the hydrolysis which the body achieves rapidly, and, having observed the progressive discoloration of our early solutions of S.C.I. and I.S. 362, we decided that a dry preparation, to be made up on the spot, was desirable. The methonium iodide dissolved aggravatingly slowly for clinical use, and we are now using the bromide as Brevidil M (methonium) and Brevidil E (ethonium).

Also, as these halides are of different atomic weight, a molecule of the chloride, for instance, will weigh less than a molecule of the bromide, although they both contain the same amount of active cation, that is, they will both paralyse to the same extent. To take a concrete example, 80 mg. of active methonium cation is contained in 100 mg. of Scoline (the chloride), but in 120 mg. of Brevidil M (the bromide), or, to put it the other way round, for paralysing purposes 100 mg. gross weight of Scoline is equal to 120 mg. gross weight of Brevidil M—they both liberate 80 mg. of active and identical cation—and I would put up a plea for the statement of dosage in terms, not of the gross weight of the drug, but of the weight of active cation, which is doing the work (*see* Table I).

TABLE I.



Bromide or Chloride is NON-ACTIVE ANION Atomic weight 79·9 or 35·5	Suxamethonium or Succinylcholine is ACTIVE CATION	Bromide or Chloride is NON-ACTIVE ANION Atomic weight 79·9 or 35·5
	Molecular weight = 290·8	

Suxamethonium bromide contains 64% ACTIVE CATION (Brevidil M)
Suxamethonium chloride contains 80% ACTIVE CATION (Scoline)
Suxamethonium iodide contains 53% ACTIVE CATION (Succinylcholine)
Suxethonium bromide contains 66·6% ACTIVE CATION (Brevidil E)
Suxethonium iodide contains 55·7% ACTIVE CATION (I.S.362)

Tubocurarine and gallamine both paralyse by what is called "a curarizing action", in contradistinction to decamethonium iodide (C 10), and these new short-acting relaxants which exert their influence by depolarization.

The train of events leading to a normal contraction of a muscle fibre is that a nerve impulse passes down the nerve until it reaches the motor end-plate. In response to its arrival, acetylcholine is released. This is attracted to, and acts on, receptors lying at the muscle membrane, effecting a change of potential, and this depolarization initiates the contraction of the muscle fibre. The curarizing agents, curare and gallamine, act by saturating the receptors at the muscle membrane and rendering them unavailable to acetylcholine. That is, acetylcholine goes on being produced and goes on being destroyed normally. The muscle fibre remains normal and sensitive to acetylcholine. It is merely that the acetylcholine cannot reach it to set off the reaction. The pistol is loaded, but the trigger cannot be pulled.

If, now, Prostigmin is given, the cholinesterase, which is destroying the acetylcholine, is inactivated. Acetylcholine therefore builds up to a concentration high enough in the end to overcome the block presented by the curare: the muscle contracts.

C 10 and the short-acting relaxants, on the other hand, behave rather like a large and prolonged dose of acetylcholine itself, by depolarizing first the muscle membrane, which is what acetylcholine

does (and of this, of course, the fibrillary twitching which occurs just after the injection is a sign), and then a narrow zone of underlying muscle tissue. They paralyse because the acetylcholine, which is being normally produced and can reach its receptors unimpeded, finds the membrane already depolarized, and no longer electrically excitable. The trigger can be pulled, but the pistol is not primed. Prostigmin is to be discouraged as an antidote, as the paralysis may be indefinitely prolonged by it.

Several points arise from a consideration of the clinical usage of the drug, which as Dr. Scurr reported (1951) we commenced using last year for the attenuation of ECT.

Firstly, none of our patients was premedicated with atropine. I have always hesitated to submit any candidate for a minor medical manœuvre (especially an out-patient) to the added (and so often unnecessary) discomfort of a dry mouth, and with these short-acting relaxants especially, the protective mechanisms of swallowing and coughing return to full vigour with such rapidity that I think it is even less justified.

The other point arises from a personal experience of the drug and concerns the provision of adequate thiopentone "cover" for the relaxant.

In the very early stage of our work on these drugs, we gave a "sleep dose" of thiopentone and followed this with the relaxant, but before long we ventured to mix them in the same syringe and no impairment of activity being apparent, this technique we adopted for the next month or two.

Then, to study and record, without the complication of the ECT, the effect of this mixed dose of thiopentone and the drug we were giving, I myself had 3 c.c. of thiopentone mixed with 75 mg. gross weight of I.S. 362 (that is, 42 mg. of the active ethyl cation), a dose which we now know is inadequate for full paralysis.

I wrote this account immediately afterwards.

"Scurr said he had injected; I would not have known this, though I felt the venepuncture, and knew he had withdrawn blood.

"A consciousness of smell followed—not the classical smell of onions, but rather the hard clean smell of the chemistry laboratory. I commented on this I think with clarity. At this time, I had no feeling of anything unusual. However, a sensation of burning tightness followed around the neck and up the back of the head, and I knew I was becoming rapidly paralysed and this I said in a voice which I realized was very slurred.

"I was now in darkness and completely paralysed—although I attempted to move, I could do nothing.

"I still had some respiratory activity and I was aware of saliva in my pharynx. There was a slight catch in my respiration which I knew had a laryngeal origin and I thought 'Scurr will be worried by that'.

"Respiratory activity was now, I think, inadequate, and the proceedings could have developed a nightmare quality—darkness, suffocation and complete inability to move.

"I heard Scurr say 'He's tough' and then, before panic set in, rather like coming out of a railway tunnel, I found that my respirations were deepening, my eyes opened and almost immediately I felt in full possession of all my power. There was no hangover—the feeling was very similar to the recovery from nitrous oxide. I had not been to sleep."

My colour had remained normal throughout. I realized from this that in the dosage I was customarily giving, the relaxant acted quicker than the pentothal, which had, however, considerably dulled my appreciation of the unpleasantness, and, although I had not been to sleep, the experience had not been too alarming.

A week later, I had a dose of 75 mg. (gross weight) of I.S. 362 without any thiopentone.

Undulled by barbiturate, I was painfully conscious of the real horror of the situation and the involuntary rapidity with which the residuum of my diaphragmatic power was exercised to maintain the maximum pulmonary ventilation possible was an index of the desperation felt.

This was a thoroughly unpleasant episode and to submit any patient to it is absolutely unjustifiable. Thereafter, I gave thiopentone first, normally 3 or 4 c.c. (150 or 200 mg.) and waited for the first deep sighing breath before injecting the relaxant from another syringe.

A few weeks ago, I once more decided to try on myself the effect of mixing the drugs, making certain this time that I went to sleep. We used 6 c.c. (300 mg.), of thiopentone and 55 mg. a.c. of Brevidil E and my account follows:

"Mask on face—quite comfortable—Scurr says 'Yes, that's fine' and I knew he had looked at the tracing. Prick on arm—no feeling in arm or shoulder and then a slow feeling of increasing warmth in back of neck and occiput—a feeling which simulated exactly the arborizing flame which one sometimes experiences on turning the head suddenly and which I attribute to nipping the roots of an occipital nerve. I thought rather grimly 'Here we go again' at which point the sensation faded and Scurr took the mask off. I said 'Carry on' (*see* Fig. 1). He replaced it but soon removed it again, and I realized that whatever had happened was over. I sat up and swung my legs over the side of the couch. Nurse made to hold me, but I said, 'No, no, let's see what I can do'. I stood unaided, buttoned the waistband of my trousers and turned round and unplugged the machine. About one minute later, I asked rather querulously who had stopped the machine."

I had, in fact, I realize now, gone to sleep almost as soon as I became conscious of the feeling of muscular stimulation and awakened calmly without realizing that I had lost consciousness, though nearly two minutes had elapsed. There was no sensation of paralysis or unpleasantness and though Dr. Scurr assures me that my twitchings and movements were considerable, I remember nothing of this. I am sure that the relaxant only raced the thiopentone by a few seconds, perhaps five, and now, assuming that one can rely on most patients having at least five or ten seconds retrograde amnesia preceding the shock, I am mixing the drugs again and giving them from the same syringe, which of course is much more convenient. I give the injection as fast as possible as I think this assures the maximum depression from a minimum of thiopentone and, as the thiopentone hydrolyses the relaxant, it is essential to mix them at the last moment.

I stress again with the utmost gravity the inadvisability of subjecting any patient to the terror of encroaching paralysis while conscious, a terror that the only patient we attempted it on remembered with distaste, despite the shock and convulsion.

Our routine technique now is to give, at the first treatment, 200 mg. of thiopentone mixed at the very last moment with 55 mg. a.c. of Brevidil E (equivalent to approximately 25 mg. a.c. or 30 mg. gross weight of Scoline), and thereafter to vary the dosage according to the phenomena observed. This dosage of relaxant is for many people at the threshold of adequacy.

Injection is followed in about twenty seconds by closure of the eyes and a deep breath. This in turn is commonly followed by generalized fibrillary muscle twitching and other semi-co-ordinated movements, a picture very similar to that presented by a moderately well-attenuated convulsion. These widespread muscular flickerings represent the onset of depolarization and their subsidence indicates the onset of the maximum paralysis for that dose. The arms and hands are often lifted towards the neck and remain in half-flexion if so lifted, till they relax and drop into extension. This coincides with the end of the muscle twitching and is the signal for the shock to be given, and it almost always happens within twenty-five to thirty-five seconds after the injection. The convulsion is usually accompanied by the appearance of "gooseflesh" and at the end the reflexes are hyperactive and the plantar response is often extensor for a short while. Respiration commences almost immediately and reaches normal excursion in about one to two minutes.

Some cases exhibited a transient slight cyanosis, but I found that oxygen was very rarely needed. For everyday practice, however, I would recommend the routine use of oxygen, and apparatus for its administration must always be to hand. In this context I would suggest that psychiatric departments employing relaxant agents should seek the advice of an experienced anæsthetist on the apparatus and technique for insufflation with oxygen.

The average patient is well enough recovered from unmodified ECT to be left untended within five to six minutes, and the actual convulsion rarely lasts more than a minute. Thus if attenuation is to be counted as a justifiable complication, full paralysis should last no longer than two minutes and should have completely receded within six. The short-acting relaxants fulfil these requirements. We have seen nothing to occasion alarm or contra-indicate their use. Their advantages over C 10, gallamine, and tubarine, which cannot be pushed to ensure first-class attenuation without the certainty of residual curarization, are, I venture to suggest, obvious, and may be graphically demonstrated by spirometric tracings. The spirometer in each case was filled with oxygen, but there was no absorption of carbon dioxide. Thus the tracings represent the maximum respiratory activity of which these patients were capable. "P" indicates the injection of thiopentone and the relaxant in each case is marked. Each tracing shows the degree of attenuation of shock and convulsion by means of "plus" signs up to 3 for "very good".

Fig. 1 is a tracing of the author (A. E.). The points to note are that 55 mg. a.c. of Brevidil E were not a full paralysing dose and that two minutes after administration I was capable of a respiratory excursion of 3 litres.

Fig. 2 shows four tracings from the same patient. "S" indicates the shock and "E" the end of the convulsion. The top tracing shows her respiratory pattern during the convulsion under thiopentone alone, that is, during a virtually unmodified convulsion.

The scale to the right of this tracing, showing the extent of an excursion of 1,000 c.c., is valid for all the figures.

The second tracing is her reaction under Brevidil E and here one may note that for her 55 mg. of active cation is a full and paralysing dose. It may be seen in the lower two tracings that dosages of Gallamine and C 10 which did not produce perfect attenuation, yet resulted in prolonged respiratory depression; this markedly so in the case of C 10.

It is interesting that the tracing of the patient undergoing unmodified convulsion is very similar to the tracing of myself under the relaxant, yet in the patient the combination of convulsion and relaxant has resulted in a slightly delayed return of adequate respiratory activity. If an excess of acetylcholine is liberated during the convulsion as Hobson and Prescott (1947) suggested, this might to some extent potentiate the Brevidil and prolong its action for a few seconds.

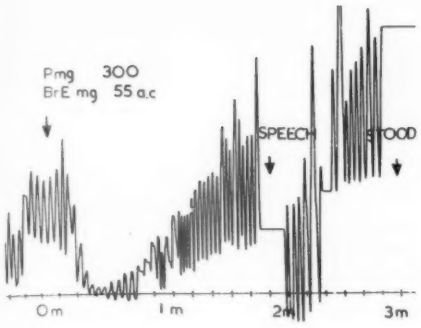


FIG. 1. — Spirometric tracing of volunteer receiving thiopentone (P) 300 mg. mixed with Brevidil E (Br. E) 55 mg. active cation. There was no shock administered. Note that paralysis was incomplete.

In all tracings timing is in minutes:
S = time of administration of shock.
E = end of convulsion.
P = thiopentone soluble 5%.
BrE = Brevidil E.
BrM = Brevidil M.
Sco = Scoline.
C 10 = decamethonium iodide.
Fl = Flaxedil (gallamine).

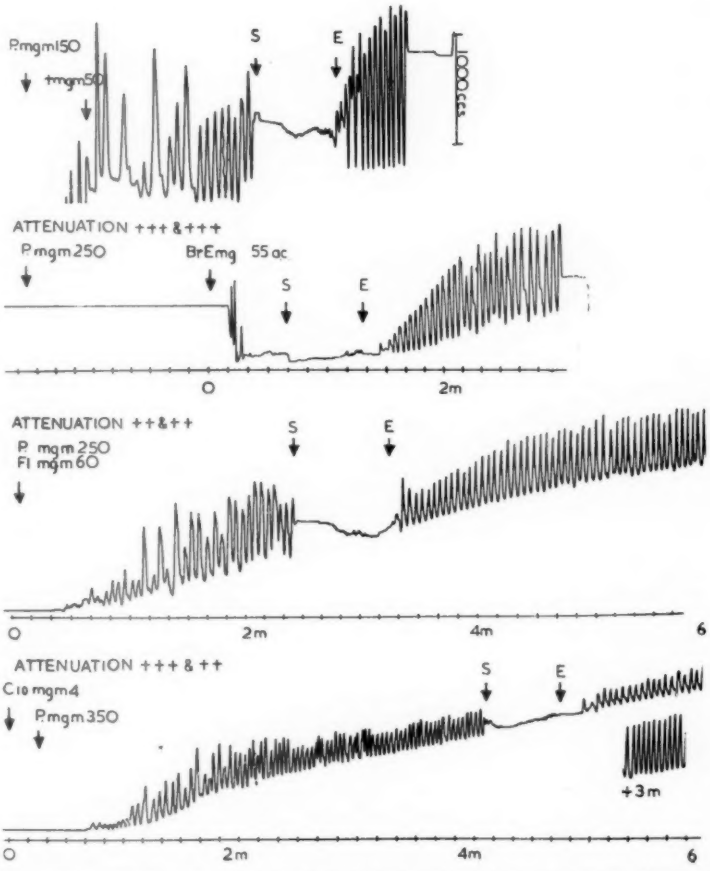


FIG. 2.—Spirometric tracings of a patient being convulsed under thiopentone alone, thiopentone followed by Brevidil E, thiopentone mixed with gallamine, and decamethonium iodide followed by thiopentone. The inset on the lower tracing shows that the respiratory excursion nine minutes following 4 mg. of C 10 was only just adequate (*circa* 500 c.c.).

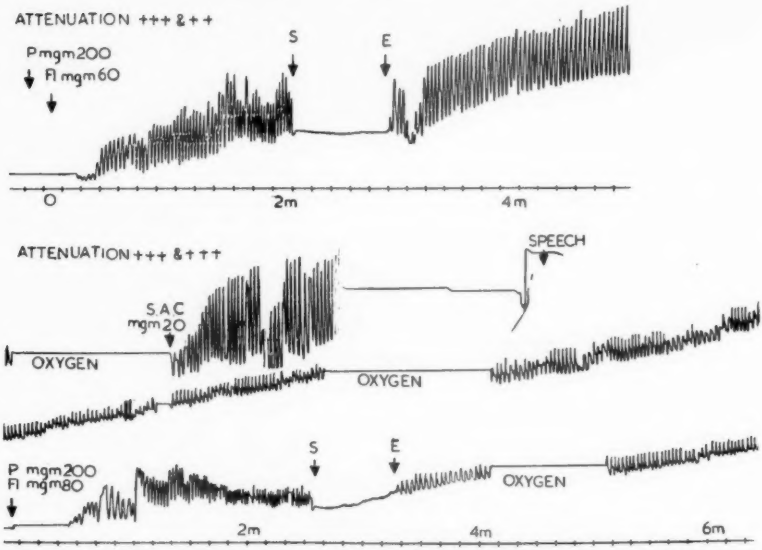


FIG. 3.—Two tracings from a patient receiving, above, thiopentone and gallamine (Fl) 60 mg. and, below, thiopentone and gallamine 80 mg. In the lower tracing, which represents three circuits of the recording drum, respiratory excursion remains inadequate until the exhibition in the fourteenth minute of 20 mg. of Tensilon (3-Hydroxyphenyl dimethylethyl ammonium chloride), S.A.C. on the tracing, when a dramatic analepsis occurred.

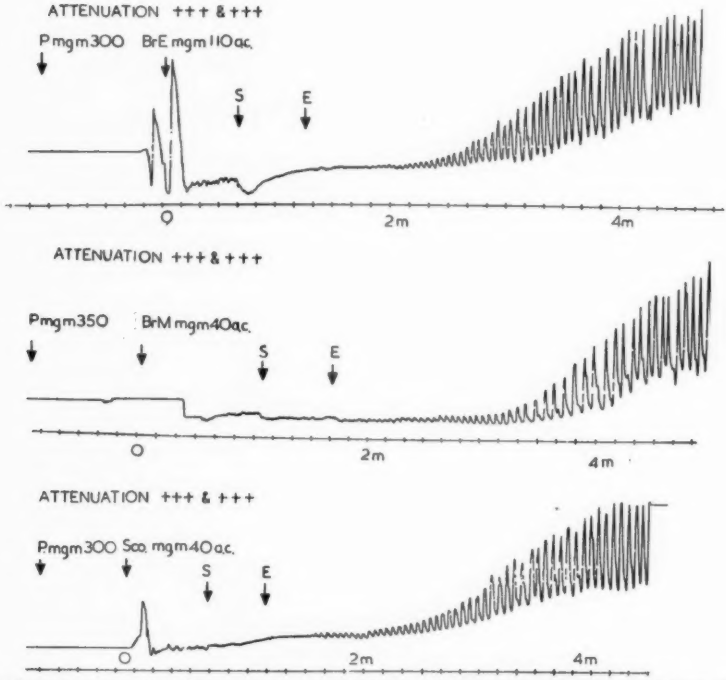


FIG. 4.—Tracings from a patient demonstrating the similarity of respiratory response to 110 mg. active cation of Brevidil E, 40 mg. active cation of Brevidil M and 40 mg. active cation of Scoline.

Fig. 3 demonstrates the danger of attempting perfect attenuation with the longer acting relaxants. In this case, the upper tracing shows the respiratory activity of a patient moderately attenuated with 60 mg. of gallamine. The increase to 80 mg. gave splendid attenuation, in every way comparable with that obtained using Brevidil. It also left us with a paralysed patient on our hands, whose behaviour agreed well with the figure of thirty minutes which Presland and Palmer (1950) gave as necessary for the recession of perfect relaxation with gallamine.

Fig. 4 (three tracings from another patient) shows that the methonium cation is approximately two and a half times as powerful as the ethonium. That is, 40 mg. of active methonium cation (as liberated by 60 mg. of Brevidil M or 50 mg. of Scoline) and 110 mg. of active ethonium cation (as liberated by 160 mg. of Brevidil E) produce a paralysis which, mirrored in respiratory activity, was identical in degree and duration.

These last tracings reflect the result of an intentional overdosage yet may be compared very favourably with overdosages of gallamine in Fig. 2, and a scarcely adequate dosage (4 mg.) of C 10 in Fig. 1, and indeed, in no case have we seen apnœa lasting longer than the three minutes mentioned by Woolley *et al.* (1942) as occurring occasionally after unmodified ECT.

BIBLIOGRAPHY

BENNETT, A. E. (1940) *J. Amer. med. Ass.*, **114**, 322.
—— (1941) *J. Amer. Psych.*, **97**, 1040.
—— (1943) *J. nerv. ment. Dis.*, **98**, 23.
BOVET, D., BOVET-NITTI, F., GUARINO, S., LONGO, V., MAROTTA, M. (1949) *R.C. ist. Sup. Sanit.*, **12**, 6.
DAVIES, D. L., and LEWIS, A. (1949) *Lancet*, i, 775.
HOBSON, J. A., and PRESCOTT, F. (1947) *Brit. med. J.*, i, 445.
——, —— (1949) *Lancet*, i, 819.
KALINOWSKY, M. B., and HOCH, P. H. (1952) Shock Treatment, Psycho-Surgery and other Somatic Treatment in Psychiatry. New York.
MAZZONI, P., and OTTOLENGHI, R. (1951) Communication to the 26th Congress of Anæsthetists, London.
NEUSTATTER, W. L., and FREEMAN, H. (1939) *Lancet*, ii, 1071.
PALMER, H. (1939) *Lancet*, ii, 181.
—— (1946) *J. ment. Sci.*, **92**, 411.
PRESLAND, R., and PALMER, H. (1950) *N.Z. med. J.*, **49**, 262.
SCURR, C. F. (1951) *Brit. med. J.*, ii, 831.
SMITH, R. H. F., and THOMAS, D. L. C. (1951) *Brit. med. J.*, i, 861.
THOMPSON, O. S., and NORTON, A. (1951) *Brit. med. J.*, i, 857.
WOOLLEY, L. F., JARVIS, J. R., and INGALLS, G. S. (1942) *J. nerv. ment. Dis.*, **96**, 680.

Dr. Audrey L. Ferguson, *Senior Registrar, Department of Psychological Medicine, Westminster Hospital*: Since August 1951, we have used the newer short-acting muscle relaxants for the modification of ECT in co-operation with the Anæsthetic Department of the Westminster Hospital. Prior to that date we had given either unmodified ECT, or where this was contra-indicated, ECT modified with either decamethonium iodide (C 10) or gallamine triethiodide (Flaxedil).

ECT either alone or modified with one of these longer-acting relaxants has two disadvantages. In the case of unmodified ECT, there is first the risk of bone injury, and second, the frequent development during treatment of a fear which makes the patient unwilling to continue the course. With regard to bone injury, Sargant and Slater (1948) noted that without newer methods of physical control 40% of patients sustained fractures, particularly compression fractures of vertebral bodies, and that this constituted the most frequent risk encountered in unmodified ECT. They recommend as a safeguard against such damage either the holding of the patient by five trained nurses or, alternatively, his insertion into a modified strait jacket before treatment: both these procedures are open to criticism.

Cook (1944) quoted the incidence of crush fractures as 4% even under the best conditions and other writers report still higher figures. The unaccountable fear which develops in some patients during treatment is quite familiar to those who have given a number of ECTs and thiopentone has been employed by Cooper (1948), Thorpe (1948) and many others to diminish this fear. For the same reason we ourselves as a routine used either thiopentone or sodium amytal intravenously in every unmodified case.

The principal disadvantages of using C 10 or Flaxedil to modify ECT are first, the uncertainty of producing perfect attenuation without considerable residual curarization, and second, the delay of from two to four minutes between the injection and the onset of maximal relaxation when the shock may be given.

The purpose of our investigation was to obtain sufficient data to compare the effectiveness of C 10 and Flaxedil with that of the newer short-acting group in the modification of ECT. As a secondary consideration we incorporated for comparison a number of cases who were given Ro 3-0386, i.e. 5 : 6-Dithiadecane-1 : 10-bis (trimethylammonium iodide), and hereafter referred to as 30386. The number of cases in whom this drug was used was limited by the small quantity available.

Investigation

The investigation was undertaken between August 1951 and May 1952; 37 cases received courses of ECT, making a total of 215 treatments in all. 30 of these treatments are excluded because of the unknown effect of subshocks and a further 8 for other reasons.

The remaining 177 treatments were as follows:

Unmodified ECT	Total = 21	*Short-acting relaxants*	Total = 105
Long-acting relaxants	Total = 51	Brevidil E	= 42
C 10	= 16	I.S. 362	= 50
Flaxedil	= 16	Brevidil M	= 7
30386	= 19	S.C.I.	= 6

Each case which had either unmodified ECT, or ECT with a long-acting relaxant, also had a short-acting relaxant. In this way we ensured that any patients with peculiarly long recovery times did not only affect adversely the results in the unmodified or long-acting relaxant group.

The points we set out to investigate were:

(1) The patients' impressions of the treatments. (2) The adequacy of the modification. (3) The time of recovery of various functions.

Results

Patients' impressions of treatments.—These were obtained by questioning each patient prior to every treatment about his recollections of the previous one. Unpleasantness prior to the administration of shock or during the recovery phase was noted.

Our first object was to discover whether the time of action of the new relaxants was so short that the amnesia resulting from ECT would be sufficient in itself to cover any known unpleasant effects of the drug, or if this were not so, whether the amount of thiopentone could be small relative to that required for the longer-acting relaxants. To this end we gave one man a set dose of 75 mg. I.S. 362 (the first of the new short-acting relaxants used by us) and reduced the dose of thiopentone accompanying it on successive occasions. As little as 50 mg. resulted in no complaints from the patient, so that with the fourth treatment we gave him no thiopentone at all. The next time he appeared very unwilling to continue the course and on questioning stated that he had felt himself unable to move, tried to fight against this sensation and had great difficulty in breathing. With return to the previous dose of thiopentone he was quite content thereafter. A second case was given 50 mg. of I.S. 362 and 150 mg. sodium amytal. She complained of feelings of suffocation and shaking all over as she went off to sleep. This latter appears to be related to the fibrillation of muscles prior to complete relaxation. As her convulsion was poorly attenuated with 50 mg. I.S. 362 we doubled the dose and gave her 150 mg. of thiopentone with it, but she again complained of similar unpleasant sensations although to a lesser degree than on the previous occasion. By increasing the thiopentone to 200 mg. we had no further complaints.

Following these preliminary trials we eventually established the average dose of each of the short-acting relaxants and found that an average accompaniment of 187 mg. of thiopentone was required to prevent the patient's having unpleasant feelings. One man to whom we gave almost twice the average dose of I.S. 362 complained of no actual respiratory difficulty, but of cold feelings and of fighting against something: these sensations did not arise when the thiopentone was increased beyond the average dose. Apart from these cases we had no other complaints in our series of 105 treatments modified by the short-acting relaxants despite the fact that in many instances the dose of thiopentone was well below average.

With the longer-acting relaxants we found that 30386 required an average adjuvant of 199 mg. of thiopentone, while with C 10 250 mg. and with Flaxedil 227 mg. were necessary, if complaints about treatment were to be avoided.

On the whole, we had few unfavourable comments from patients with any of the relaxants. Even with the longer acting C 10, 30386 and Flaxedil there were only single instances with each drug in which a patient complained of suffocation or vague fears when the accompanying thiopentone was given in dosages above the average for that particular relaxant. Two on 30386 complained with average doses of thiopentone. With those in whom thiopentone was below average we had no complaints in the 30386 series, two complaints with C 10 and two with Flaxedil.

In the Flaxedil series we had two or three patients who had severe headache and nausea or vomiting following treatment. Most interesting of all, however, was one patient who was able to pick out his Flaxedil treatments from those with Brevidil E, Brevidil M, C 10 and I.S. 362. He was given more than the average dose of thiopentone with less than the average amount of Flaxedil, while the short-acting relaxants and their thiopentone were given only in average doses. In his distinction he said, referring to Flaxedil treatments: "I wake with a severe headache to find myself struggling and as if I want to climb up the walls." With the other drugs he said that he awoke feeling back to normal and could have got up at once, if required to do so; whereas after Flaxedil this would have

been impossible. From the objective point of view his recovery after short-acting relaxants and C 10 was always quite smooth; after Flaxedil he fought and struggled with us for a considerable period of time before he could be moved into the recovery room. It is also of interest that with Flaxedil and C 10 modification of his convulsion was markedly less satisfactory than with the short-acting relaxants.

Adequacy of modification.—In order to determine our second point we considered both the attenuation of the initial jerk or "shock" and also that of the subsequent convulsion. To do so we laid down criteria similar to those already used by Davies and Lewis (1949) in their paper comparing C 10 and *d*-tubocurarine, which subdivided the modification of the convulsion into three degrees.

Our criteria were as follows:

Modification of "Shock"

+++	(*Good*)	No movement except possibly a twitch of the face.
++	(*Moderate*)	Slight twitch of shoulders or other parts of the body, the back excepted.
+	(*Poor*)	Fairly severe twitch with the back included.

Modification of Convulsion

+++	(*Good*)	Movements of facial muscles including platysma. If any large joints were moving their movements required to be slight and with no power—no back movements were allowed.
++	(*Moderate*)	Large joint, facial and minimal back movements present.
+	(*Poor*)	Marked back movements, though with some modification. No modification at all was scored if powerful back movements were present.

These measurements were recorded in 98 treatments with the short-acting relaxant group, 16 with Flaxedil treatments, 18 with 30386, and 15 with C 10. In the short-acting group 52% of the patients obtained "good" modification for both the shock and convulsion at the same treatment, while with Flaxedil there were none, 28% with 30386, and 13% with C 10. It seems, therefore, that the new relaxants act quickly enough to cover the period of shock and remain effective long enough to modify the convulsion. Fig. 1 illustrates the relative proportions of "good", "moderate" and "poor" results for shock and convulsion considered independently.

With regard to subshocks, we found there was always time to re-shock and still to obtain "good" or "moderate" attenuation. 2 of our cases were not re-shocked until 105 sec. following injection,

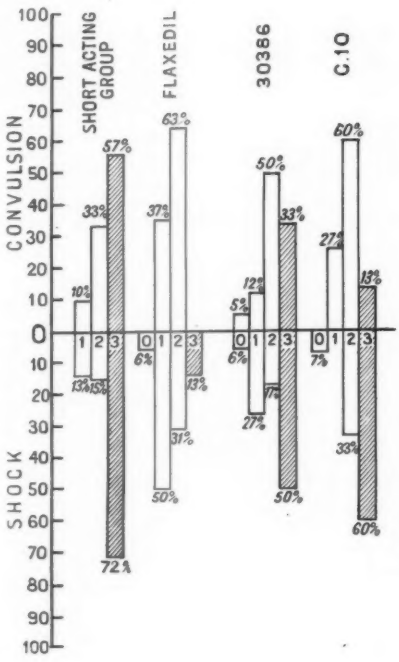


FIG. 1.—Chart to illustrate percentage of treatments showing the various degrees of attenuation of shock and convulsion.

0 = No attenuation.
1 = Poor attenuation.
2 = Moderate attenuation.
3 = Good attenuation (hatched area).

but still showed triple + attenuation. The remainder of these cases showed that up to 70 sec. after injection one may be sure of "good" modification, but thereafter this degree of attenuation is more uncertain.

Time of recovery of various functions.—The last assessment made was a comparison between the duration of the effects of (*a*) the short-acting relaxants, (*b*) unmodified ECT and (*c*) the longer-acting 30386, C 10 and Flaxedil.

Ideally, the important stages in the recovery phase would be when respiration had returned to a level where anoxia was no longer a danger; when the patient could safely be left unattended; and when he was fit to leave hospital. Since these stages are too indefinite for any accurate measurement, four points in the recovery phase were chosen as being relatively unambiguous in their times of occurrence and as giving a good indication of the duration of the drug's effects.

(1) Return of respiration: the first spontaneous breath.

(2) Return of muscular activity: the first movement of a part of the body as opposed to contraction of isolated muscle groups, e.g. turning of head or movement of toe or finger were accepted while blinking or rhythmic champing of jaws was rejected.

(3) Return of speech: Any intelligible response was accepted. During both this stage and the previous one, the patient was stimulated verbally but by no other means.

(4) Fitness to leave. The following criteria had to be fulfilled before fitness to leave was accepted: (*a*) The ability to stand and walk without any inco-ordination. (*b*) The ability to dress without assistance. (*c*) Correct orientation.

These times were recorded from the injection of the drug except in the case of unmodified ECT when of necessity they had to be taken from the induction of shock. The interval between injection and shock was kept relatively constant and at the optimal time for each drug. In order to make results comparable, the mean interval between injection and shock for the short-acting relaxants was added to all the unmodified ECT times.

The results for I.S. 362 and Brevidil E were closely alike in every way and the differences were of no significance. They were therefore combined for comparison with the longer-acting drugs. Fig. 2 shows these results in diagrammatic form.

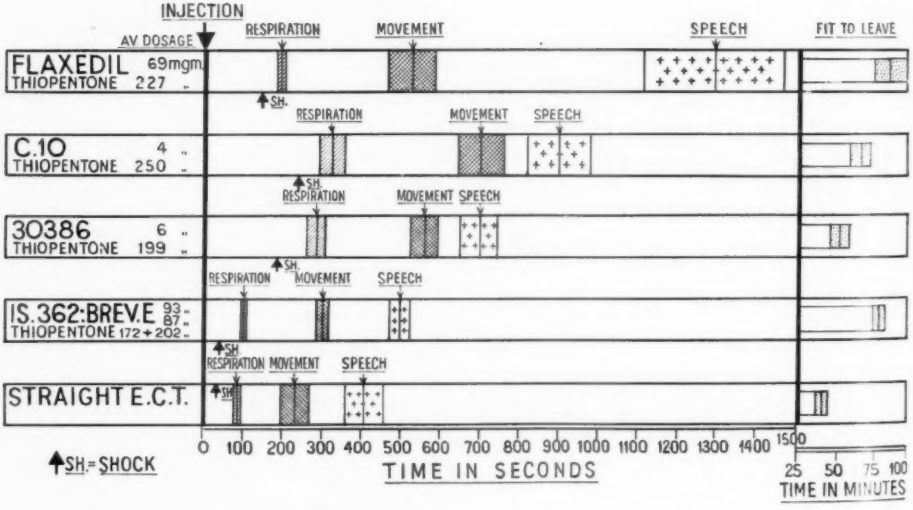


FIG. 2.—Chart showing mean times from injection to stages of recovery in diagrammatic form. (Shaded areas represent standard error of the mean.)

Except for the anomalous results in the times of fitness to leave which are discussed later, unmodified ECT showed the quickest recovery at all stages, as might be expected. The differences between these and the times for the short-acting group were small and analysis of the figures showed them to be of no great significance; while all the others showed greater differences which were in each instance highly significant. Since the shock was given much sooner after injection of the short-acting drugs than with the longer-acting ones, it seemed possible that we were measuring the time taken for recovery from the effects of ECT given at varying times after the injection, and not intervals

attributable to the drug itself. When, however, the times were measured from induction of shock, the relationship between the short-acting group and unmodified ECT remained, of course, unaltered. With the other drugs the respiration times, while still being slightly greater than that of the short-acting group were no longer of any significance.

This suggests that return of respiration assessed by this method is dependent upon the apnœic effect of the shock—little modified by the drug. Such a result was to be expected since respiration never entirely stopped prior to induction of shock except with the short-acting group. In the latter apnœa was the rule and it is noteworthy that despite this there was no increased delay in the return of respiration. The differences for muscular activity and speech persisted, and, with the exception of speech in the case of 30386, remained significant though to a lesser degree. Another possible explanation for the differences lies in the slightly higher dose of thiopentone required with C 10 and Flaxedil, but for practical purposes if it is necessary to give a larger dose of thiopentone it is of no great importance whether the delay is due to the relaxant or the thiopentone.

To give some idea of the extent to which this modifies recovery times, the coefficient of correlation between dosage of thiopentone and recovery of muscular activity was calculated in the I.S. 362 cases. This showed a positive correlation of $0{\cdot}25 \pm 0{\cdot}056$. When this figure was used for all results in the muscular activity group, it meant that the increased average dose of thiopentone contributed 8·4 secs. to 30386 times, 52·5 secs. to C 10 times and 35 secs. to Flaxedil times. The differences still remained but their significance became slightly less.

In the results for fitness to leave the recovery time for the short-acting group was significantly longer not only than unmodified ECT but also than 30386 and C 10. It was a little shorter than Flaxedil but not significantly so.

This is both surprising and difficult to reconcile with consistently contrary results indicated by the return of muscular activity and speech.

Other observations made during the course of treatment lend support to the view that the result was due to some extraneous influence and not to the effect of the drug. Firstly, in many cases given 30386, C 10 or Flaxedil, there was noticeable curarization when speech returned while in the short-acting group, this was so in only one case when a considerable overdose of I.S. 362 was given. Secondly, the time at which patients were able to get up and walk with assistance was noticeably sooner with the short-acting group than with either C 10 or Flaxedil. This time was only measured in 8 of the short-acting group, when the mean was 9 min. With Flaxedil 4 cases showed a mean of 18 min., and 2 cases of C 10 a mean of 21 min. In their series Davies and Lewis stated that most cases of C 10 were able to walk with assistance 30 min. after treatment. Since the assessment of fitness to leave both presents difficulties in measurement and is open to innumerable unknown or little appreciated influences and since the time was decided by different members of staff it is possible that by then none of the drugs were exerting any influence and the difference depended on variations in the interpretation or application of the criteria laid down. It is difficult to explain on this premise why the differences should be significant. But once the anomalous times became obvious this possibility was investigated. The criteria were re-emphasized, and great care was taken that they were uniformly applied. 43 cases were treated with short-acting relaxants, and the mean time for fitness to leave was 75·1 min., which showed no discrepancy from the series as a whole. The explanation therefore remained unknown, but the fact that the Flaxedil results showed a similar delay in fitness to leave is possibly significant, since they were obtained at a later date following the re-emphasis of the criteria. A further 6 cases of C 10 also done at this stage had a mean time for fitness to leave of 77·3 min., but the numbers were too small for any conclusions to be drawn.

Conclusions

(1) The short-acting relaxants are fully effective in a much shorter time than Flaxedil, C 10 or 30386, and the depression of respiration caused by them is of sufficiently brief duration to make oxygenation an exceptional rather than routine procedure.

(2) With the short-acting relaxant group in doses sufficient to produce adequate attenuation of both shock and convulsion, recovery to a point at which medical supervision is no longer necessary is quicker than with other relaxants.

(3) With all relaxants unpleasant effects can be avoided by giving an adequate dose of thiopentone, which dose is slightly smaller for the short-acting relaxants.

References

Cook, L. C. (1944) *J. ment. Sci.*, **90**, 435.
Cooper, J. F. (1948) *Brit. med. J.*, ii, 879.
Davies, D. L., and Lewis, A. (1949) *Lancet*, i, 775.
Sargant, W., and Slater, E. (1948) Physical Methods of Treatment in Psychiatry. Edinburgh.
Thorpe, F. J. (1948) *Brit. med. J.*, ii, 998.

I am deeply indebted to Dr. Geoffrey Lomas, Clinical Assistant to the Department of Psychological Medicine, Westminster Hospital, for his invaluable help in the statistical analysis of our results.

LIST OF BOOKS RECEIVED FOR REVIEW

(*As no reviewing is undertaken in the "Proceedings" this list is the only acknowledgment made of books received for review*)

Jones (E. P.) Kielland's forceps. pp. x + 212. London: Butterworth's Medical Publications. 35s. 0d. 1952.

Stambul (J.). The mechanisms of disease: a study of the autonomic nervous system, the endocrine system and the electrolytes in their relationship to clinical medicine. pp. xxxiv + 746. New York: Froben Press. $15.00. 1952.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Churchill (E. D.). Obliterative bronchitis and bronchiectasis. pp. 23. London: Institute of Child Health. 1952.

Colyer (Sir Frank). Old instruments used for extracting teeth. pp. 245. London and New York: Staples Press. 42s. 0d. 1952.

Houston (W. V.)., et al. The scientists look at our world. pp. 147. Philadelphia: University of Pennsylvania Press. $3.00. 1952.

Visher (S. S.). Scientists starred 1903–1943 in "American Men of Science". pp. 556. Baltimore: Johns Hopkins Press. 1947.

Weber (F. P.). On nævi and miscellaneous subjects. pp. 72. London: Lewis. 12s. 6d. 1952.

Worster-Drought (C. C.), ed. Residential speech therapy. pp. 150. London: Heinemann. 15s. 0d. 1952.

Clinical Section

President—HAROLD EDWARDS, C.B.E., M.S.

[*May* 9, 1952]

MEETING HELD AT QUEEN MARY'S HOSPITAL FOR CHILDREN, CARSHALTON, SURREY

Poliomyelitis: Nursing and Rehabilitation of Cases

Dr. C. D. Agassiz, discussing the importance of the correct nursing method for children suffering from poliomyelitis, said:

The child should lie flat in bed with the feet in the correct position as for standing. This position was maintained by means of a footboard, which not only kept the feet in position but also raised the bedclothes off the limbs. No pillows were permitted until all the tightness of the tissues had disappeared; treatment, however, should be carried out daily. When they were able to sit up they should sit in an adapted chair—not in bed. Splints and plaster casts do not prevent deformity and to illustrate this point Dr. Agassiz showed photographs (Figs. 1, 2 and 3).

Directly the child could put his feet to a right angle he should be allowed to stand with support and from then onward the physiotherapist would put him through the routine movements of standing, walking and so on.

In these cases the great point was the prevention of residual deformity. Any muscle power which remained should be induced to function as soon as possible. Stretching after hot packs or hot and cold sprays should be continued until all tendency to tightness had disappeared.

FIG. 1.—Splints on which patient in Fig. 2 arrived. Apparatus to prevent deformity modified Jones's frame. Plaster for legs. Perspex splints for arms. Spinal jacket.

FIG. 2.—Showing deformity after splinting.

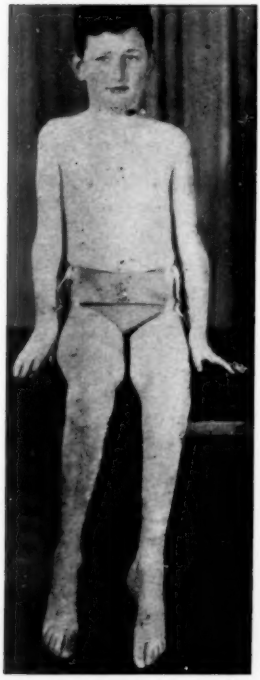


FIG. 3.—Same boy after hot packing and stretching had eliminated the tightness.

Streptomycin in the Treatment of Bone and Joint Tuberculosis

Mr. R. H. Metcalfe (Consultant Orthopædic Surgeon) showed 10 cases of proved bone and joint tuberculosis, treated with streptomycin and para-aminosalicylic acid (PAS).

The treatment of tuberculous arthritis of the hip at Queen Mary's Hospital for the ten years before the introduction of streptomycin therapy can be summarized as follows:

Hip: Traction on a Pugh's frame for twenty months. Plaster spica for ten months. Plaster spica, raised boot on good leg and crutches six months. Celluloid spica until considered safe to discard (average twelve to twenty-four months).

Knee: Immobilization on a Pugh's carriage twenty months. Plaster fixation ten months. Celluloid knee splint and patten-ended Thomas's splint twelve months. Weight bearing in celluloid splint until safe to discard (average twelve months).

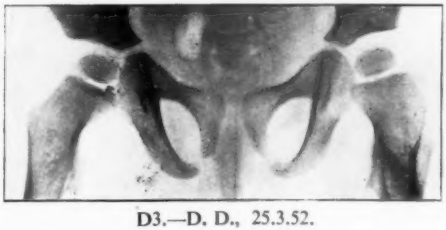
A1.—P. W., 11.7.49.

A2.—P. W., 17.11.49.

A3.—P. W., 8.2.52.

D1.—D. D., 4.7.51.

D2.—D. D., 1.8.51.



D3.—D. D., 25.3.52.

Spine: Immobilization on Pugh's carriage twenty months. Plaster fixation twelve to twenty-four months according to level of lesion in spine. Celluloid splint until safe to discard (twelve to twenty-four months).

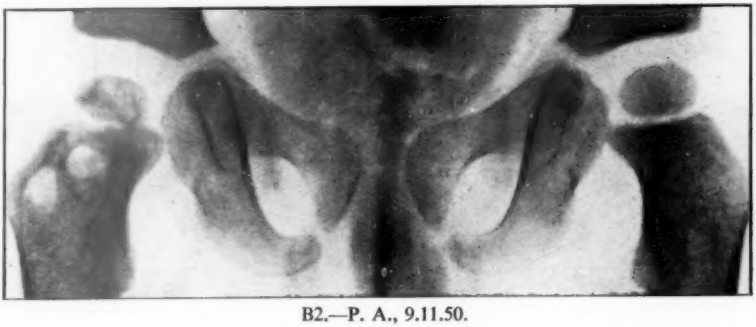
Shoulder: Immobilization of abduction splint twenty months.

Tarsus: Plaster fixation fifteen months. Celluloid splint and patten-ended Thomas's splint twenty-four months.

Streptomycin and PAS therapy was instituted at Queen Mary's Hospital in the early months of 1949, and most of the cases shown had been under observation for three years. Treatment was started as soon as the diagnosis had been confirmed. The dosage used was as follows:

Age	Streptomycin	PAS
1– 5 years	$\frac{1}{4}$ gramme b.d. = $\frac{1}{2}$ gramme daily	$\frac{1}{2} \times 6 = 3$ grammes daily
5–10 ,,	$\frac{3}{8}$ gramme b.d. = $\frac{3}{4}$ gramme daily	$1 \times 6 = 6$ grammes daily
10–15 ,,	$\frac{1}{2}$ gramme b.d. = 1 gramme daily	$2 \times 6 = 12$ grammes daily

B1.—P. A., 23.6.50.



B2.—P. A., 9.11.50.

B3.—P. A., 5.12.51.

The duration of treatment was ninety days so that a child aged 6 would receive 68 grammes of streptomycin and 540 grammes of PAS. Occasionally a second course has been given after an interval of 90 days.

Streptomycin is given by injection into the thighs, and PAS by mouth mixed half and half with undiluted orange cordial. No case of deafness or any other vestibular effects occurred, possibly due to the fact that only calcium chloride streptomycin and not di-hydrostreptomycin was used.

Abscesses were present in all patients except Case A. In cases D and F the abscesses were opened and streptomycin was injected into the abscess cavity. There were no instances of sinus formation. There was gross bone destruction in all the cases, but the so-called "joint space", made up by the epiphyseal cartilages, remained intact, except in the patient with tuberculous arthritis of the spine (Case E).

The first effect of streptomycin, as shown in all X-rays, is a great decrease in the degree of bone density and this would appear to be due to immediate increased vascularity around the lesion. This is followed in one to three months by a characteristic "walling-off" of the lesion by a layer of dense bone (Cases A2, B2, and C2) which presumably prevents further spread of the disease. Next, as

C1.—J. H., 29.12.49.

C2.—J. H., 29.6.50.

C3.—J. H., 8.1.52.

the child grows, new bone is laid down outside this delimiting layer (Cases A2, B2, and F2). Finally the lesion inside the delimiting layer recalcifies and the lesion disappears (Cases A3, B3, C3, D3, and F3).

Abscesses are absorbed with great rapidity, in many cases without the need for incision or aspiration (Cases B, C, E, and F). In Case D the abscess cavity was "saucerized" and filled with streptomycin. The incision healed by first intention and the lesion disappeared in seven months. In Case E, the abscess disappeared in the X-ray in twelve months and complete bony fusion of the vertebral bodies was present in fourteen months. Of considerable interest and importance is the reformation of bone in apparently completely destroyed epiphyses and metaphyses with preservation of the "joint space" and movable joints (Cases B, C, and F). In the 10 cases shown movable joints were present in all except the spinal case (Case E).

The results after two years' experience with streptomycin and PAS appeared so promising that hopes arose that it might be possible to reduce the period of immobilization at the various stages of treatment.

E1a.—R. C., 18.7.50.

E1b.—R. C., 18.7.50.

E2a.—R. C., 25.9.51.

E2b.—R. C., 25.9.51.

Unfortunately, at least 4 patients, in a series of 100 treated with these drugs, have developed secondary lesions in other parts of the skeleton during the period of immobilization. It is therefore clear that no reduction in the duration of treatment can be permitted.

In the past, especially in hip cases, the aim of the surgeon was to obtain a bony arthrodesis in the affected joint, so as to avoid risk of reactivation. Now with the help of streptomycin and PAS, movable joints are being obtained. It remains to be seen if reactivation, probably with a resistant organism, will occur.

The question of resistant organisms is one of increasing importance, since streptomycin is now used extensively in the treatment of phthisis. It is well known that the incidence of bone and joint tuberculosis is steadily decreasing in this country and elsewhere, due to pasteurization of milk, T.T. herds and the earlier diagnosis and treatment of open tuberculosis. There appears to be a real danger, however, that streptomycin-resistant strains of the tubercle bacillus will become more numerous and that within a matter of a few years there will be a great increase in the number of cases of bone and joint tuberculosis.

F1.—D. G., 28.9.49.

F2.—D. G., 21.4.50.

F3.—D. G., 11.4.51.

With this in mind, treatment with Pycazide (nicotinic acid hydrazide) was started at Queen Mary's Hospital in April 1952. The effects of treatment with this drug are being carefully studied with particular emphasis on blood levels, blood counts, toxic effects (especially on the kidney and nervous system), and the formation of resistant strains. It is still too early to express an opinion on the results of treatment but in 2 patients infected with resistant strains, the E.S.R., which was between 45–50 mm. in the first hour (Westergren) for several months, has fallen to 5 mm. within three weeks of the administration of Pycazide. There has also been a marked increase in appetite and well-being and disappearance of pain.

In view of the danger of streptomycin-resistant tubercle bacilli, it must be hoped that Pycazide will help in the future treatment of these cases, but it must be remembered that *in vitro* resistance to Pycazide develops in eight days.

Treatment of Rheumatic Carditis

Dr. C. E. Thornton showed selected patients who were under treatment in the Rheumatism Unit. All the patients had had active rheumatic carditis, some with gross valvular damage. The condition, as shown by the E.S.R., E.C.G., and clinical findings, was quiescent.

Dr. Thornton pointed out that some of the patients had been treated only by absolute rest in bed, some with aspirin, one of them with chloromycetin and one with ACTH. Notwithstanding this difference in treatment, the periods in which signs of active carditis persisted were much the same for all the patients. The only common factor in the treatment was absolute rest.

Dr. Thornton said that he was not prepared to assert that the course of rheumatic carditis was not affected by drug treatment. However, these results emphasized the fact that in rheumatic infection it was difficult to be sure how far any particular treatment influenced the course of the disease.

Arthrodesis of Tuberculous Hips

Mr. R. Glyn Thomas: The standard to be aimed at in the end-result of treatment of a tuberculous hip should be to ensure a permanently safe and useful limb for the patient.

The first lines of treatment are early and prolonged immobilization, with antibiotics, e.g. streptomycin and PAS, given as adjuncts. If, after this treatment, the radiographs still show that there is destruction of the articular surface of the femoral head or acetabulum and if, after consideration, the possibility of a useful, permanently safe and painless range of movement is doubtful, then arthrodesis of the hip is probably the best policy.

The optimum position for final ankylosis in children after recalcification is: Adduction 5 degrees; rotation—slight external 5 to 10 degrees; flexion 10 to 15 degrees. (Various types of arthrodesis performed on children at Queen Mary's Hospital were shown.)

(1) *Ilio-femoral arthrodesis.*—Advantage of this operation is that it is comparatively easy to perform. It causes little post-operative shock with few complications (*see* Case I).

(2) *Brittain's arthrodesis* (*ischio-femoral*).—I usually do this type of arthrodesis when I have to correct adduction or flexion deformity (*see* Cases III and IV).

(3) *Ischio-femoral arthrodesis posterior approach.*—I usually perform this operation through a large window cut out posteriorly in a double hip spica plaster which has been applied before operation. The graft is taken from the tibia. The leg from which the graft is taken is always put in plaster, even if it be taken from the sound leg.

The graft is inserted through the osteotomy of the femur with the medullary surface of the graft facing downwards. The lower end of the shaft of the femur at the osteotomy site is, if possible, displaced inwards to support the middle of the graft. The double hip spica is left on for four months and then a single hip spica is applied for a further four months (*see* Case II).

Case I.—Tuberculosis of Right Hip:

P. B., male, aged 20.

Onset of disease, 1942.

Readmitted Q.M.H. September 1943 with flare-up of hip. Treated until 1947 and at that time

CASE I.

FIG. 1.—13.3.45.

FIG. 2.—27.9.48.

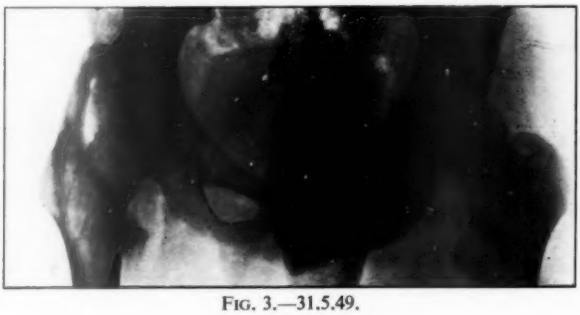


FIG. 3.—31.5.49.

there was a firm fibrous ankylosis in the hip-joint, and considerable bone loss and deformity of the femoral head and acetabulum.

Readmitted September 1948 with further flare-up. Was put in double hip spica for two months and then ilio-femoral extra-articular arthrodesis of the right hip was performed, the indication for operation being repeated flare-ups.

In March 1949 there was clinically sound bony fusion.

Discharged from hospital July 1949—hip firmly ankylosed—B.S.R. Westergren 3 mm. per hour. Walking well.

CASE II.

FIG. 4.—19.7.46.

FIG. 5.—8.7.48.

FIG. 6.—3.3.52.

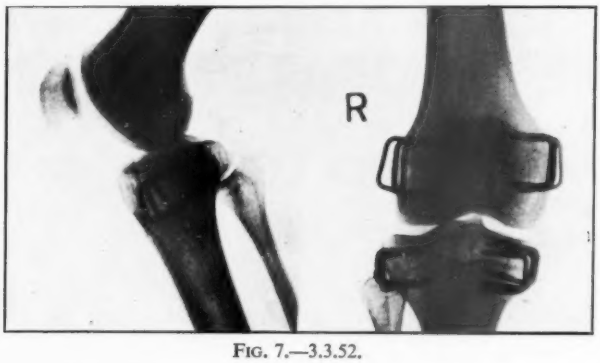


FIG. 7.—3.3.52.

Case II.—Osteomyelitis of Left Hip.

J. B., girl, aged 15.

Long history of osteomyelitis of hip going back to 1946. Treated at various times with traction, removal of sequestra, &c. Finally discharged June 1947, wearing a caliper.

Readmitted three weeks afterwards with osteomyelitis. She had further flare-ups and when seen in October 1948 had a fibrous ankylosis of the left hip with a rocking movement only. There were considerable changes in the head of the femur. In view of repeated flare-ups and unstable fibrous ankylosis, ischio-femoral arthrodesis was performed through a posterior approach on 11.5.49.

Discharged 20.12.49 with sound fusion of the left hip clinically and radiologically. Approximately 3 in. of true shortening.

When seen in June 1950 there was sound fusion in 15 degrees abduction and slight external rotation. There was 3 in. of true shortening. As this was increasing, it was decided to staple the opposite knee.

Stapling right knee 20.9.50.

When seen in March 1952 there had been no further trouble with the left hip. True shortening now 3 in. X-ray showed all epiphyses of right knee fused. As staples are producing no further effect, arrangements have been made to remove them in the near future.

Case III.—Tuberculosis of Right Hip.

R. N., male, aged 18.

Admitted December 1945 with T.B. right hip. Was treated on a Pugh's frame and then plaster. When discharged from hospital there was a fibrous ankylosis of the right hip with a rocking movement. X-ray showed considerable destruction of the head of femur.

Readmitted 16.3.49 with reactivation. He had an unstable fibrous ankylosis of the right hip and in view of the history of reactivation, arthrodesis was decided upon.

22.4.49: Brittain type arthrodesis of the right hip-joint performed.

On discharge November 1949 there was sound bony union in neutral adduction/abduction. True shortening ½ in. He has remained well since operation.

CASE III.

FIG. 8.—5.9.47.

FIG. 9.—10.3.49.

FIG. 10.—4.12.50.

Case IV.—Tuberculosis of Right Hip.

W. M., boy, aged 10.

First admitted Q.M.H. 22.7.46 and treated on hip frame and carriage until June 1949.

In February 1947 he developed an abscess of the medial side of the thigh which was treated by repeated aspirations and ultimately healed.

9.11.49: Ischio-femoral arthrodesis through posterior approach. Decision to arthrodese hip was taken because of unstable fibrous ankylosis with destruction of head and adduction deformity. The graft shifted during application of the plaster and it was later found that the medial end of the graft had not fused with the ischium.

When discharged from hospital in December 1950 there was firm fibrous union of the right hip with $\frac{1}{2}$ in. of true shortening.

He attended After-Care Clinic at regular intervals and it was noted that a flexion deformity of the right hip was developing. In 1951 this was 50 degrees. In view of this increasing deformity and of the fact that there was only a fibrous ankylosis of the hip, it was decided to perform a Brittain's ischio-femoral arthrodesis. Operation on 23.5.51 with graft taken from tibia of same side. Flexion deformity corrected osteotomy site.

Discharged home 4.11.51. Sound bony union of right hip in slight flexion and abduction. True shortening $\frac{3}{4}$ in.

CASE IV.

FIG. 11.—9.10.47.

FIG. 12.—17.5.51.

FIG. 13.—9.9.51.

Section of Orthopædics

President—PHILIP WILES, M.S., F.R.C.S.

[*April* 1, 1952]

The Syndrome of Forefoot Instability

By R. C. F. CATTERALL, F.R.C.S.

APPROXIMATELY one-fifth of all the patients who come to our clinics complaining of their feet will be found on examination to wear their shoes out in an identical and highly characteristic manner. This shoe-wear (Fig. 2, B and C) is well known as part of the clinical picture of hallux rigidus, but its frequent occurrence without gross stiffness of the great toe is worthy of note. I consider this wear to be a sign not of hallux rigidus so much as of an unstable fore-foot—a deformity which itself is the cause of all hallux rigidus other than those attributable to direct trauma to the joint.

The wear, which is extremely rapid and heavy, is of the outer side of the heel and sole, and of that part of the sole which lies directly below the tip of the great toe. The upper is wrung over to the inner side but the creases in the toe-cap will not be found until the ultimately inevitable hallux rigidus has made its appearance.

FIG. 1.—Feet and Shoes. Age 3.

Patients showing this wear will be found in every age group. The 5-year-old of either sex is frequently brought along by its mother because she has noticed that it "walks flat-footed". The child does not complain, but often proves, though just as active, to be less agile than its playmates. The feet collapse into valgus under load, but the paradox that such feet cause wear of the outer side of the heel does not appear to have aroused the interest one would have expected (Fig. 1).

The 10-year-old occasionally complains of pain on exercise, but more commonly is picked out at a routine inspection. The feet still collapse into valgus and the full extent of the deformity of the fore-foot may be revealed by simple inspection (Fig. 2A). The shoe-wear is typical, and by the age of 13 a notable degree of degenerative arthritis of the metatarsophalangeal joint may have developed. Such arthritis is always associated with fatigue pain which is the dominant clinical feature in the later age groups. In children the sex incidence is equal, but in young adults females greatly outnumber males. This altered sex incidence I believe to be due to two factors: the use of high-heeled court shoes which often proves the critical factor in determining a flare of the arthritis, and pregnancy with its sudden addition to the load placed on these unstable feet.

In the fifth and sixth decades mild degrees of the deformity may cause severe symptoms for the first time although fatigue pain of only nuisance value has often been present for years (Fig. 3, A and B). The appearances of feet and shoes are basically identical with those seen in the infant.

The essential deformity in all these feet is a supinating twist of the fore-foot. Its occurrence in the very young postulates a congenital origin, as does its existence among barefooted races. Some of the symptoms may be made worse by the use of badly designed shoes.

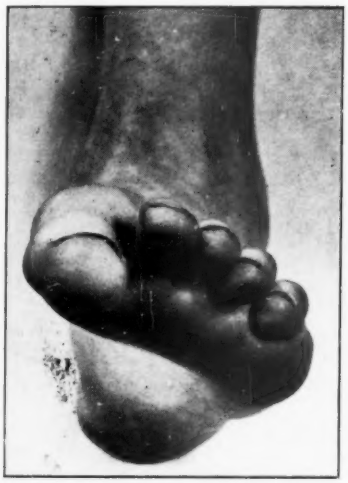


FIG. 2A.

FIG. 2B.

FIG. 2C.

FIG. 2 (A, B and C).—Foot and shoes. Age 10.

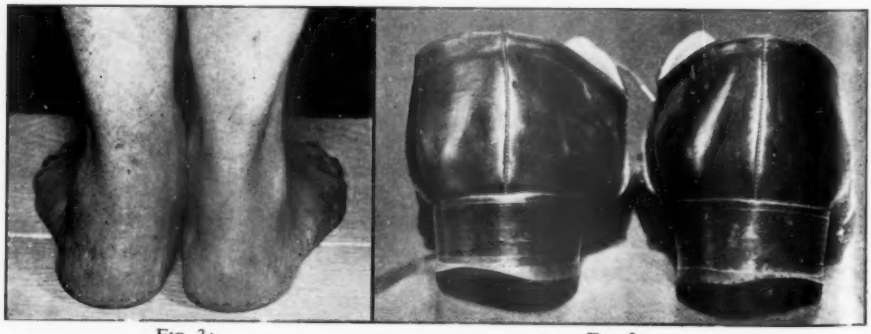


FIG. 3A. FIG. 3B.

FIG. 3 (A and B).—Feet and shoes. Age 60.

The production of the arthritis of the great toe-joint is brought about in one of two ways (*see* Fig. 4). The rest-position of the foot allows weight to be borne only on the os calcis and the head of the 5th metatarsal. As the load is increased one of two things can happen: either the whole foot collapses into valgus until stability is attained, or else the big toe is flexed to produce the needed tripod support.

The first alternative splays out the metatarsals and encourages the development of hallux valgus: the second causes a weight-bearing thrust across the metatarsophalangeal joint which it was never meant to withstand. Hallux flexus et rigidus is the inevitable sequel.

In considering treatment one must first enquire how many of the children would recover spontaneously if treated expectantly. It is apparent that a high proportion would do so, although many may have minor "foot morbidity". I know of no clinical sign by which the favourable case may be diagnosed with certainty and it therefore follows that each case must be treated actively from the beginning. Treatment is conditioned by the presence or absence of a degenerative arthritis. Before it develops the object is to correct the deformity by manipulation and then encourage normal muscular action to prevent a recurrence. The passive correction is always easy, but the muscle re-education is difficult. Voluntary pronation of the fore-foot is very hard to perform, and the production of pronation by electrical stimulation contra-indicated alike by its technical difficulty as by its unpleasantness. The commonly used flat-foot exercises are worse than useless as they serve only to increase the existing deformity. It therefore seems that the use of an appliance is essential.

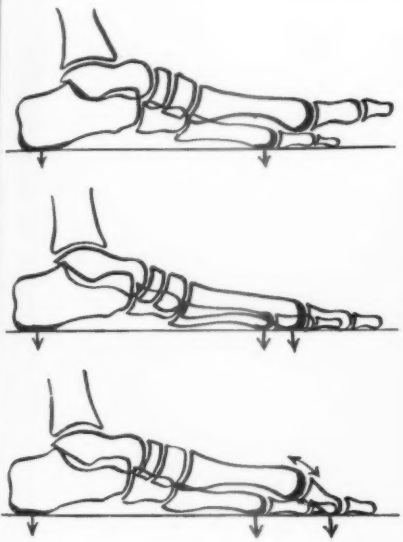


FIG. 4.

FIG. 5A and 5B.

FIG. 4.—Diagram to show mechanism of production of symptoms.

FIG. 5.—A and B. Spring pronating device.

Various appliances are available; a wedge may be added to the outer side of the sole and a stiffener placed to hold the hind-foot level. Alternatively an insole may be made with a cavity under the first metatarsal head into which the bone may be hoped to descend under load. Both these devices have two disadvantages. They make the shoe unduly stiff and heavy, and, more important, they are effective only during the act of weight-bearing. They are, however, foolproof and the "contra-wedge" in particular is often effective in minor degrees of deformity. For more severe cases a more permanent corrective force is necessary, and this may be provided by the addition of a spring to the shoe (Fig. 5). A coil of spring wire, between 18 and 22 gauge according to the size of the shoe, is laid in the instep and protected from wear and tear by a tin shield. The outer end of the spring is anchored in the heel, and the inner end cranked upwards and forwards. Opposite the 1st metatarsal head it is attached to a strap, which, lying across the metatarsal heads, is fastened to the outer side of the welt. A valgus stiffener ensures that the twisting force is localized to the mid-tarsal region. The effect is pronation of the shoe (and the foot), at rest, but enough elasticity remains to allow normal activity.

This device has been in use for nearly two years, and is well tolerated by all patients whose feet are still mobile. Clinical experience suggests that its use should be continued for at least a year after barefoot stability has been regained to diminish the likelihood of a relapse.

The pressure of the spring proves intolerable to children in whom passive correction is hard to attain. Manipulation of these feet under anæsthesia, followed by plaster splinting in the over-corrected position for three weeks, will often allow treatment to proceed.

Feet which show an established degenerative arthritis cannot be expected to respond to conservative measures alone. Any surgical attack in early adult life should be directed both at the arthritis of the joint and at the deformity of the 1st metatarsal which caused it. For these reasons I prefer the combined Keller-and-osteotomy operation to the simple fusion of the tarso-metatarsal joint described by Jack in a paper read before the British Orthopædic Association in September 1951. In elderly patients symptoms will be completely cured by a simple arthroplasty of the joint.

SUMMARY

A syndrome of foot disability due to congenital supination of the fore-foot is outlined and its relationship to the production of hallux rigidus discussed.

Various methods of treatment are compared with the use of a new device to pronate the fore-foot. This device is easily made and has given encouraging early results.

Mr. J. S. Batchelor: Many young children have a valgus foot posture which is frequently but erroneously called "flat foot", and which causes wear on the shoes similar to that described by Mr. Catterall. Such a posture is perfectly normal during the toddling years, and in most children disappears spontaneously about the age of 6 or 7. It is quite unnecessary to waste the time of these children and their parents on useless exercises. I do not believe that hallux rigidus is predisposed to by the valgus foot or, indeed, by any of the various abnormalities of the first metatarsal to which it has been attributed by different authorities. Hallux rigidus usually develops in the long and rather rigid foot with a large hallux, and is due in the majority of cases to trauma, either recurrent or acute, to the first metatarsophalangeal joint. The development of hallux rigidus is followed at an early stage by a flexion deformity of the joint with secondary elevation of the first metatarsal. The Keller operation without metatarsal osteotomy gives excellent results when properly carried out.

Mr. W. Sayle-Creer said that in America Morton (1935) had drawn attention to defects of the first metatarsal, calling a short metatarsal *metatarsus atavisticus*, and to the unstable metatarsal under the term *hypermobile first metatarsal segment*. Lambrinudi (1937) had advocated correction of the permanently elevated first metatarsal, which he called *metatarsus primus elevatus*, by an osteotomy and bone graft. This procedure had later been modified by T. T. Stamm, whose curved osteotomy was very effective. Jack (1940) of Edinburgh had pointed out the association of hallux rigidus with postural defects of the first metatarsal. It was very convenient to lump these three defects under the title *the incompetent first metatarsal segment*. It was important to use the word "segment" because the internal cuneiform was involved as well as the first metatarsal. In some cases the inner three metatarsals and the cuneiforms were all affected and then the condition was the *supinated fore-foot*.

Treatment depended on whether we were attempting to correct the deformity or deal with the results of the deformity. Hallux rigidus cannot be cured by osteotomy, an operation such as Keller's being necessary. In some cases it was useful to combine the osteotomy with Keller's operation, in order to correct the primary defect. Whatever operation was done on the child's foot, he, Mr. Sayle-Creer, was very firmly of the opinion that it should not interfere with movements of joints. He was insistent that ablation of joints in the child's foot was a very bad procedure, though the problem was different in the adult. In all cases where fore-foot instability was a primary cause of trouble, it was most important to assess the case meticulously, so that the correct procedure was carried out, and again he wished to stress that whatever treatment was given it should leave the patient with mobile joints.

REFERENCES

JACK, E. A. (1940) *Brit. J. Surg.*, **27**, 492.
LAMBRINUDI, C. (1937) *Proc. R. Soc. Med.*, **31**, 1273.
MORTON, D. J. (1935) The Human Foot; Its Evolution, Physiology and Functional Disorders. New York.

Clinical Applications of the Functional Anatomy of the Lower Back [*Summary*]

By W. F. FLOYD, Ph.D., B.Sc., F.Inst.P., A.M.I.E.E., J. S. R. GOLDING, F.R.C.S., and P. H. S. SILVER, M.B., Ph.D.

Middlesex Hospital

THE phenomenon of flexion relaxation of the erectores spinæ takes place when the vertebral column is fully flexed in standing and sitting (Floyd and Silver, 1951*a*, 1951*b*, 1952). The intervertebral ligaments play the dominant role in maintaining trunk posture in full flexion.

Electromyographic studies on patients suffering from back trauma showed that flexion relaxation does not occur after injury to the intervertebral ligaments (e.g. supraspinous, interspinous ligaments, or the intervetebral discs). The study of muscle movement patterns provides therefore a useful adjunct in the diagnosis of back injuries, and valuable objective evidence in assessing response to treatment and progress of cases of backache.

REFERENCES

FLOYD, W. F., and SILVER, P. H. S. (1951*a*) *Lancet*, i, 133.
——, —— (1951*b*) *J. Anat., Lond.*, **85**, 433.
——, —— (1952) *J. Anat., Lond.* (In the press.)

Section of Epidemiology and State Medicine

President—Professor ROBERT CRUICKSHANK, M.D., F.R.C.P., D.P.H.

[*January* 18, 1952]

DISCUSSION ON THE CAUSES OF ABSENCE FROM SCHOOL

Dr. E. R. Bransby: Each child in this country throughout his school life has on average almost a year's absence from school. Absence records can be used to reduce the volume of avoidable absence, and, perhaps more important, for the selection of children who require medical or social examination.

The Extent and Causes of Absence

Information on school absence in this country comes mainly from a study made in 1947/8 in Kesteven (Lincs), Worcestershire, Birmingham and Sheffield in which records were kept for 9,444 children for one year. In Birmingham and Sheffield the children included attended schools in four distinct types of neighbourhoods, namely, slum, new housing, working class and good class (Bransby, 1951). Table I shows the incapacity rates in the different groups studied.

TABLE I.—AVERAGE PERCENTAGE RATES AND RANGES IN INCAPACITY

Type of Incapacity	Up to 7 years				8–11 years				12 or more years			
	Boys		Girls		Boys		Girls		Boys		Girls	
	Av.	Range	Av.	Range	Av.	Range	Av.	Range	Av.	Range	Av.	Range*
Total ..	11·3	8·4–14·9	11·2	8·9–14·4	8·2	6·1–16·0	8·3	5·6–11·2	7·3	5·2–10·0	9·1	5·6–13·8
Medical ..	9·8	6·9–13·3	9·7	7·6–12·8	6·6	4·9–12·7	6·6	4·2– 8·4	5·3	3·8– 7·7	6·3	3·1– 9·3
Medical, less C.I.D.† ..	6·7	5·3– 7·6	6·9	6·0– 8·1	5·8	4·5–12·2	5·9	3·8– 7·8	5·1	3·7– 7·7	6·1	3·0– 9·1
Non-medical ..	1·5	1·1– 1·9	1·5	0·9 –1·8	1·6	1·1– 3·3	1·7	0·9– 2·8	2·0	1·4– 3·0	2·8	1·4– 4·7

*These values are the ranges for the *groups* studied, e.g. children attending schools in slum, working class areas, &c. They show the wide variations in incapacity rates among *groups* of children of the same sex and age.

†C.I.D. means the common infectious diseases.

Medical incapacity, less that due to the common infectious diseases (C.I.D.), was about 15% greater in Birmingham and about 25% greater in Sheffield in social class V compared with social classes II–IV. The causes of non-medical incapacity were a clear reflection of social conditions. Thus among children attending schools in poor neighbourhoods, absence due to domestic work predominated, while in the good neighbourhoods, absence due to holidaying with parents predominated. For social class III children medical incapacity less that due to the common infectious diseases was about 40% greater and non-medical incapacity about 30% greater among children attending schools in poor districts compared with that for children attending schools in good districts. There is thus a substantial "neighbourhood" factor as distinct from a "social class" factor.

Children having more crowded homes had about 15% more medical incapacity (less that due to the C.I.D.) than did children having less crowded homes. The relationship with family size varied with age. The rates of medical incapacity (less that due to the C.I.D.) for children aged under 7 belonging to families with two children, was 80–85%, and with three or more children 70–75%, of that of "only" children. For older children, the rate for boys belonging to families with three or more children was about 115% and for girls about 120% of those for "only" children. For non-medical incapacity the rate for older girls belonging to larger families was about 125% of that for girls belonging to larger families.

Absence was markedly associated with the standard of parental care. Incapacity, for example, among older girls and boys was practically double where the parents were disinterested in schooling compared with where the parents were interested. Where the mother went out to work both medical and non-medical incapacity were substantially lower than where the mother did not go to work. The reduction in non-medical incapacity was greater for older girls and where there were large families. Working mothers probably found it inconvenient to keep the children at home.

Data collected in one year's study in Stoke and Salford in 1943/4 (Bransby *et al.*, 1946) showed that incapacity rates in Salford exceeded those in Stoke by about 9–16% at 5–7 years, 57–59% at

8–10 years and 74% (boys) and 96% (girls) at 12 or more years. Incapacity was 30–40% greater among children with bad than among those with good homes, and about 15% more in Salford and 30–40% more in Stoke among children graded "poor nutrition" compared with those graded "good nutrition".

The few data on individual children suggest that they conform to certain patterns of behaviour. Downes (1945) concluded that the health of the school child was a problem highly concentrated in certain families: Norris (1951) in this country found that some children were more prone to sick absence than others. The 1947/8 study (Bransby, 1951) showed that children more frequently absent for medical reasons were also more frequently absent for non-medical reasons, and vice versa.

The Proper Level of Absence

The aim should be to reach that level of attendance most conducive to the well-being of the child. This might not be the highest possible level. Absence for non-medical reasons, excluding that due to holidays with parents, in the 1947/8 study averaged about two days per year for children up to 12, about two and a half days for older boys and four and a half days for older girls. These averages, however, hide wide variations between children. Thus a group of older girls who belonged to large families and had indifferent parents were absent almost one-quarter of the time for medical reasons and over one-sixth for non-medical reasons. Although the amount of avoidable non-medical absence may on average seem small, it is a serious problem for particular groups, such as older girls coming from bad homes.

It is difficult to assess the proper level of sick absence. Obviously a sick child should not attend school nor a well child stay at home. Study is required to determine to what extent children attend school when not really fit. Sick absence might be reduced by earlier exclusion from school of children with coughs, colds, sore throats, and other conditions which spread.

Methods of Reference for Medical or Social Investigation

Absence records simply relate to those conditions which, in the opinion of the parents, warrant withholding the child from school; in some cases the parents act on medical advice. Much of the information is symptomatic and based on lay diagnosis, and is of the same kind as that obtained in surveys of sickness in which data are collected by lay persons from lay persons. The question arises as to the usefulness of absence records for selecting children requiring medical or social care. Despite the limitations of the data, the following criteria for selection are suggested.

(1) *Absence for any reason for long periods.*—The object is twofold. The first is to find children with illnesses which require follow-up care or treatment. There could be a routine reference of children absent, say, six weeks or more, or children absent for long periods for specific conditions. The second is to check children absent longer than may seem necessary for particular conditions. Thus, in the 1947/8 enquiry some children were absent six weeks or more with conditions such as impetigo, scabies, debility, anæmia and quinsy.

(2) *Absence due to particular conditions.*—In order not to refer the less serious cases a minimum length or frequency of absence might be set. Examples of the conditions for which children might be referred are: ringworm, scabies, allergic disorders, diabetes, certain psychiatric disorders, migraine, certain eye conditions, cardiovascular disorders, impetigo, eczema, asthma, flat feet, and debility. In the 1947/8 study of the 9,444 children 15 were absent 5 or more times from asthma, 4 from certain ear conditions and 6 from debility. Ferguson and Cunnison (1951) reported that of the regular school attenders, 9·4% were convicted at court between the ages of 8 and 17 years, the corresponding figures being 15·9% for irregular attenders due to domestic factors, and 39·1% for irregular attenders due to truancy. Children who are absent due to serious domestic trouble or who truant frequently should thus also be referred.

(3) *Frequent absence for any reasons.*—Of the 9,444 children in the 1947/8 study 38 were absent 20 or more times for medical reasons and 26 were absent 20 or more times for non-medical reasons. Over 6% of all children were absent 15 or more times for all reasons. The absence history of two children frequently away are shown below.

Age	No. of absences	Medical	No. of absences	Non-medical
GIRL				
5	23	Vomiting, 4; bronchitis, 2; cold, 5; enteritis, 1; influenza, 1; bronchial catarrh, 3; bilious, 1; gastritis, 1; headache, 2; sore knee, 2; fall, 1	17	Overslept, 13; wet clothing, 1; no shoes, 1; truanting, 2
BOY				
12	7	Sprained ankle, 3; giddy turns, 4	25	Errands, 11; domestic work, 4; no shoes, 4; minding baby, 6

The question is the clinical significance of such histories and whether the children deserve medical examination and observation.

Form of Absence Records

The following are suggested as being practicable under particular conditions.

(i) Complete records of all absences as collected in the 1947/8 study with the information recorded on a card, such as suggested by Norris (1951) for each child. The longer the record is kept, the more instructive it becomes.

(ii) Records of children falling into the categories (1), (2) and (3) already mentioned. Teachers would need to ascertain the reasons for all absences, but only record if the child was absent for any of the selected reasons.

(iii) Children would be referred on the basis of their absence as recorded in school registers.

REFERENCES

BRANSBY, E. R. (1951) *Med. Offr.*, **86**, 223, 237.
——, BURN, J. L., MAGEE, H. E., and MACKECHNIE, D. M. (1946) *Brit. med. J.*, ii, 767.
DOWNES, J. (1945) *Amer. J. publ. Hlth.*, **35**, 593.
FERGUSON, R., and CUNNISON, J. (1951) The Young Wage Earner. London.
NORRIS, V. (1951) *Brit. J. soc. Med.*, **5**, 145.

Dr. D. D. Reid: *The personal factor in sickness absence among school children.*—The study of differences between children in the frequency of absence from school because of sickness may be of practical as well as of theoretical interest. It has been suggested, for example, that if we could detect the child whose record showed that he was absent unduly often, we could, by appropriate treatment, reduce his absence rate to within normal limits. Such a suggestion implies that there are, in fact, real differences between children in their sickness liability. It also implies that this excessive personal liability is a permanent characteristic of the individual; if it varied widely from year to year, there could be no reasonable basis for treatment or control. For such control to have a rational basis, we must know whether this liability of certain individuals to have many absences is quite general to all causes or whether it is specifically confined to a particular group of diseases. Some of the differences in sickness frequency between children must result from the random nature of their contacts with infection in home, street or school and some from difference in immunity, and epidemic exposures in the two sexes at different ages and in different calendar years. Only if, once these other factors have been taken into account, there remains a large proportion of the total variability apparently due to differences in personal liability, will it be worth while trying to pick out the "absence-prone" child from among his class-mates. In short, we need to find out whether differences in liability exist, whether individuals are relatively constant in their liability, and whether such liability is specific in nature and sizable enough to be of practical importance.

An attempt to answer these questions was made by an analysis of the sickness experience, over a period of three years, of children in three London schools which served as "controls" in a recent field trial.

Ever since the publication of the work by Greenwood and Woods (1919) on "accident-proneness", it has become almost traditional to study the differences in susceptibility between individuals by comparing the actual distribution of accidents or sicknesses among a group of individuals, exposed to the same risks over the same period of time, with distributions based on alternative theoretical assumptions. If, for example, the curve describing the distribution of numbers of children with 0, 1, 2, 3, &c., absences agreed better with a theoretical expectation based on a hypothesis of "unequal liability" than with one derived from a purely chance distribution of sicknesses among the group, it might be inferred that certain children were "sickness-prone". The practical difficulties of this approach have been pointed out (Adelstein, 1952). Gafafer and Doull (1933) applied the method to the frequency of colds in the same group of students over a three-year period; the results conflicted with the suggestion of constant differences in susceptibility implicit in the significant correlation found between the frequency of a student's colds from one year to the next. To the same data, Wilson and Worcester (1944) applied the technique of analysis of variance and confirmed the latter verdict. Their analysis took no account of other factors such as age and sex which affect susceptibility to disease; the present study includes some measurement of the relative importance of these factors and the interaction between them, and extends beyond respiratory infections to other major causes of absence among school children.

Eight randomly selected samples, each of 30 children, were drawn from the records of pupils of the same sex and age group who were attending these three schools over the whole three-year period. For each child was recorded the number of absences in each year due to each of the four major causes:

(1) Acute specific infectious fevers—measles, mumps, chickenpox, &c.—taken as a single group.
(2) Infections of the respiratory tract and accessory sinuses including the ears.
(3) All other medical causes of absence.
(4) Non-medical or social causes of absence.

The average number of absences per person in each year was calculated for the 30 children in each age-sex group, e.g. the 30 boys aged 6 in the first year of the survey had on the average 2·4 respiratory infections in Year 1 and Table I shows similar values for all age-sex and year groups.

TABLE I.—DISTRIBUTION OF FREQUENCY OF ABSENCE—MEAN NUMBER OF ABSENCES

Respiratory Absence Group

		Year 1	Year 2	Year 3	Total	
MALES	Age 6	2·4	1·4	1·8	1·9	1·7
	7	1·6	1·7	1·8	1·7	
	8	1·8	1·3	1·4	1·5	
	9	2·1	1·4	1·5	1·7	
FEMALES	Age 6	3·0	2·0	2·1	2·4	1·8
	7	1·5	1·5	1·7	1·6	
	8	1·8	1·4	1·3	1·5	
	9	1·4	1·6	1·7	1·6	
	Year totals	2·0	1·6	1·7		1·7

Inspection of the various totals will show how this arrangement of the data brings out the essential features. Thus the effect of age is evident in the difference between the frequency of absence between the 6-year olds and the rest, while the relative unimportance of sex difference is suggested by the equality of the male and female mean number of attacks. Year to year differences, on the other hand, seem to be rather more important. In all these comparisons, we need make no major assumptions or adjustments. Comparisons between the sex means, for example, can be made with confidence since each mean is based on the experience of two groups balanced for age and years of epidemic exposure.

The second advantage of this arrangement is that we can use the technique of analysis of variance to separate out and test the statistical significance of the differences associated with such factors as sex, age or years of epidemic experience and of the interaction between them. But even more relevant to the present problem is the possibility it affords of estimating the variability in absence experience due to apparent differences between individuals.

The position may be illustrated graphically as in Fig. 1. A male aged 6 in year 1 of the survey might be expected to have roughly the same average number of respiratory affections as boys of the same age in the same year. If, however, he is in fact "absence-prone", he will tend to have consistently more absences than average in each of the three years. But apart from this consistent difference, his number of absences will vary from year to year in a purely random fashion. From the size and direction of these random deviations, we can estimate the significance and importance of the consistent difference between him and the age-sex-year average. If the child has consistently more absences than average, i.e. if he appears to be "absence-prone", the size of that consistent difference will be appreciably greater than the chance year to year variation. In general, differences in personal liability exist where children differ among themselves appreciably more than might be expected on the basis of the average random year to year changes in the number of absences in the same child.

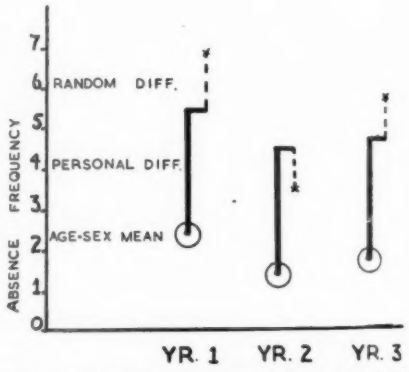


FIG. 1.—Diagrammatic reproduction of method of analysis.

The same ideas apply to the assessment of the statistical significance of the various factors involved in the incidence of the four groups of cause of absence; we compare the variance associated with them with the appropriate residual random variance. At the same time we can also assess the importance of any interactions between these factors. A significant interaction between "age" and "years" occurs when children of different ages react differently to epidemic changes from year to year. In Table I, for example, the range of difference in frequency of attack "between years" is greater for children aged 6 than for the less susceptible children of 7 and over. It should be noted that "age" here refers to children aged 6, 7, 8 and 9 in Year 1, who are followed as a "cohort" through the next two years. Table II shows the detailed analysis for respiratory infections. The results and those of similar analyses for the other causes of absence are summarized in Table III where the significance of the "personal" factor is estimated by comparing the variance "between children" with the residual "within children" variance.

As one might expect, age is a significant factor and "years" do differ one from another in their epidemic experience, while "sex" differences appear to be unimportant in all causes of absences. Our main interest at the moment is in the "personal factor" which seems to affect the incidence

TABLE II.—ANALYSIS OF VARIATION IN ABSENCE DUE TO RESPIRATORY DISEASE

	Source of variation	Sums of squares	D.F.	Mean square	Variance ratio
BETWEEN CHILDREN	Sex	1·07	1	1·07	0·22
	Age	39·21	3	13·07	2·72*
	Age and sex ..	10·30	3	3·43	0·71
	Residual	1,115·64	232	4·81	(3·36)†
	Total	1,166·22	239	4·88	
WITHIN CHILDREN	Years	21·23	2	10·62	7·45†
	Years and sex ..	1·67	2	0·83	0·59
	Years and age ..	20·28	6	3·38	2·37*
	Years, age and sex	8·67	6	1·44	1·01
	Residual	661·49	464	1·43	
	Total	713·34	480	1·49	
	Grand total	1,879·56	719	2·61	

*Significant $P < 0.05$. †Highly significant $P < 0.01$.

NOTE.—Transformation of raw data to $\sqrt{x + \frac{3}{8}}$ gave similar results.

TABLE III.—SIGNIFICANCE OF FACTORS AFFECTING ABSENCE

Factors	Absence group: Fevers	Resp.	Others	Non-medical
Sex	—	—	—	—
Age	××	×	—	—
Years	××	××	×	×
Age and years ..	××	×	×	—
Personal ..	—	××	××	×

— not significant. × significant $P < 0.05$. ×× highly significant $P < 0.01$.

of all causes of absence except the specific infectious fevers. This means that the distribution of these infectious illnesses as a group is at random among this homogeneous population of suburban school children; there is no evidence of "fever-proneness" in certain children in any age-sex group. As a useful by-product of the analysis, we can make rough estimates of the percentage of the total amount of variation in each cause of absence due to the "personal" factor or "differences in absence-liability" between children. "Personal" differences account for none of the variability in sickness absence from infectious fevers, for 27% and 34% of the "non-medical" and "other medical" groups and for 44% of the variability in respiratory infections.

TABLE IV.—CORRELATION OF ABSENCE FREQUENCY BY CAUSE IN SAME INDIVIDUAL

	Respiratory	Others	Non-medical
Respiratory ..	0·65	0·28	0·22
Others		0·58	0·26
Non-medical ..			0·52

Since "absence-proneness" appears to exist for some causes, we need to know whether it is a permanent characteristic of the child and whether it is specific to the cause.

Table IV suggests these answers to such questions:

(1) A *high* correlation between the number of absences suffered by the same child for the same cause in successive years indicates that liability is a fairly constant personal attribute.

(2) Although there is a tendency for an excessive number of absences of one kind to be associated in the same individual with an excessive number of another, the correlation is not so high as that for the same cause in the same child in successive years. This means that although there is probably what the psychologists might call a "general factor" operating to increase liability to all kinds of absence in the same child, the liability is largely specific in nature.

Finally, how might these results be used in practice and to what effect?

If we take the respiratory causes of absence as likely to be the most fruitful, we might pick out from among the children in each age and sex group in the first year the 36 children with four or more absences due to respiratory illness. In the next year, we can see how many of those 36 children remain in this apparently "respiratory-absence-prone" group, and how many had improved. Table V shows that although there is a fairly large overlap, some 64% of the 36 whom we might have considered to be "absence-prone" have reverted to the "good record" group. On the other hand, we have correctly picked out only 36% of those who had four or more absences in the second year. From these and related facts two practical conclusions emerge.

TABLE V.—COMPARISON OF ABSENCE FREQUENCY IN SUCCESSIVE YEARS

		No. of absences in year 2		
		<4	4+	
No. of absences in year 1	<4	185	19	204
	4+	23	13	36
		208	32	240

(1) It might be worth while picking out for special attention, say at a routine medical examination, those who were in the worst 20% of absentees in the previous year. Among them one would be likely to find a group with consistently bad records. But it would be unwise to classify them all as prone to respiratory infection and do something drastic, such as tonsillectomy, about it: after all, there is more than a 50 : 50 chance one may be wrong.

(2) Too often, results of treatment such as tonsillectomy are assessed without adequate control comparisons; yet three good reasons appear from this analysis to make some lessening in the frequency of respiratory illness almost inevitable. Not only does the number of absences appear to decrease slightly as the child grows older, but the significant interaction between "years" and "age" suggests that a high incidence of illness in one year does have some effect, presumably by immunization, on differences between children of different ages in the next. Together with the purely random differences between the frequency of illness in the same child from year to year, these factors may produce, as in the present example, a drop of one-third in the attack rate among the apparently "worst" 20% between one year and the next. The need for caution and control in therapeutic or prophylactic trials in this field is thus clear.

So far discussion has been confined to absence from day school where many differences in home environment and maternal or medical care may affect the reported incidence of illness. "Personal liability" measured on such data may not, therefore, truly represent differences in individual physique or temperament. Less suspect from this point of view are records of admissions to the sanatorium among children continuously housed under constant conditions in a boarding school for children deprived of parental care. The records of randomly selected children, 12 of each sex and aged 6 or 7 years at entry to the school, were scrutinized for a period of seven years. An analysis made of the frequency of all causes of admission, of which the bulk were respiratory, gave the results seen in Table VI. Except for the lack of difference between the two age-groups, or cohorts, the results resemble those already obtained. Even in these more closely controlled circumstances, personal differences in liability to sickness appear.

TABLE VI.—ANALYSIS OF VARIATION IN FREQUENCY OF ADMISSION TO SCHOOL SANATORIUM (*All causes*)

	Source of variation	Sum of squares	D.F.	Mean square	Variance ratio
BETWEEN CHILDREN	Sex	0·58	1	0·58	0·28
	Age	0·96	1	0·96	0·46
	Age and sex ..	1·20	1	1·20	0·58
	Residual ..	91·69	44	2·08	(2·08)†
	Total	94·43	47		
WITHIN CHILDREN	Years	54·57	6	9·10	9·10†
	Years and sex ..	14·50	6	2·42	2·42*
	Years and age ..	16·79	6	2·80	2·80†
	Years, age and sex	14·30	6	2·38	2·38*
	Residual ..	264·98	264	1·00	
	Total	365·14	288		
	Grand total	459·57	335	1·37	

*Significant $P < 0.05$. †Highly significant $P < 0.01$.

In summary it may be said that although disparity in age and epidemic experience have important effects on absence frequency, compared with purely chance variation, there seem to be real differences between children in liability to sickness in general and to respiratory infection in particular. This does not apply to the specific infectious fevers as a group. These differences appear to be constant, specific and important enough for their further study to be of potential value in the care of the health of school children.

REFERENCES

ADELSTEIN, A. (1952) *J. R. statist. Soc.*, **115**, 354.
GAFAFER, W. M., and DOULL, J. A. (1933) *Amer. J. Hyg.*, **18**, 712.
GREENWOOD, M., and WOODS, H. M. (1919) Industrial Fatigue Research Board, Report No. 4. London, H.M.S.O.
WILSON, E. B., and WORCESTER, J. (1944) *Science*, **99**, 468.